WHY DO DEPRESSION AND ANXIETY SYMPTOMS CO-OCCUR ACROSS DEVELOPMENT?
THE ROLE OF GENES, ENVIRONMENTS AND COGNITION

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WHY DO DEPRESSION AND ANXIETY SYMPTOMS CO-OCCUR ACROSS DEVELOPMENT? THE ROLE OF GENES, ENVIRONMENTS AND COGNITION

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ABSTRACT

Depression and anxiety commonly co-occur and have been associated with cognitive biases and executive function deficits across development. Twin studies indicate considerable genetic overlap between internalizing symptoms and cognitive processes. However, relatively little is known about how genetic, environmental and cognitive processes contribute to the co-occurrence of depression and anxiety symptoms over time.

Twin modelling analyses were conducted using three longitudinal population-based twin samples – ECHO, G1219 and TEDS. The first half of this thesis focused on developmental associations between depression and four different anxiety symptom clusters. First, the phenotypic and genetic structure of symptoms was examined cross-sectionally in childhood, adolescence and young adulthood. Developmental differences in the aetiology of the relationship between depression and anxiety were found, with genetic influences becoming less disorder-specific from adolescence. Next, longitudinal analyses found that both stable and newly emerging genes, and to a lesser extent non-shared environmental effects, contributed to the co-occurrence of depression and anxiety across adolescence and young adulthood.

The second half of this thesis focused on cognitive processes involved in the aetiology and maintenance of depression and anxiety. First, associations between anxiety sensitivity dimensions and depression and anxiety symptoms were investigated. Results identified disorder-specific versus shared cognitive content in depression and anxiety that was generally unchanged across development and was underpinned by broad genetic vulnerability. Second, association between mindfulness, anxiety sensitivity and depression was investigated. Mindfulness was found to be moderately heritable and the relationship between attentional control aspect of mindfulness, depression and anxiety sensitivity was largely due to shared genetic liability. Finally, using an experimental study conducted in sixty-one 8-10 years old children, depression and anxiety were found to be independently associated with poorer attentional control. This attentional deficit may account for some of the attentional biases often observed in anxious and depressed children on tasks investigating processing of emotional stimuli.

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POEM

A Contribution to Statistics

by Wislawa Szymborska

Out of a hundred people

those who always know better

— fifty-two

doubting every step

— nearly all the rest,

glad to lend a hand

if it doesn't take too long

— as high as forty-nine,

always good

because they can't be otherwise

— four, well maybe five,

able to admire without envy

— eighteen,

suffering illusions

induced by fleeting youth

— sixty, give or take a few,

not to be taken lightly

— forty and four,

living in constant fear

of someone or something

— seventy-seven,

capable of happiness

— twenty-something tops,

harmless singly, savage in crowds

— half at least,

cruel

when forced by circumstances

— better not to know

even ballpark figures,

wise after the fact

— just a couple more

than wise before it,

taking only things from life

— thirty

(I wish I were wrong),

hunched in pain,

no flashlight in the dark

— eighty-three

sooner or later,

righteous

— thirty-five, which is a lot,

righteous

and understanding

— three,

worthy of compassion

— ninety-nine,

mortal

— a hundred out of a hundred.

Thus far this figure still remains unchanged.

From *Poems New and Collected*, by Wislawa Szymborska / Translated by Stanislaw Baranczak

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All work in this thesis is original and is my own work, except as acknowledged in the text.

Monika A Waszczuk

PUBLICATIONS RESULTING FROM WORK FROM THE CURRENT THESIS

Waszczuk, M. A.*, Zavos, H. M. S.*, Gregory, A. M., & Eley, T. C. (2014). The phenotypic and etiological structure of depression and anxiety disorder symptoms in childhood, adolescence and young adulthood. *JAMA Psychiatry, 71*(8), 905-916.

Waszczuk, M. A., Zavos, H. M. S., Gregory, A. M., & Eley, T. C. (2015). The continuity and change of aetiological influences on depression, anxiety symptoms and their co-occurrence across adolescence and young adulthood. *Psychological Medicine.* First View.

Brown, H. M.*, **Waszczuk, M. A.***, Zavos, H. M. S., Trzaskowski, M., Gregory, A. M., & Eley, T. C. (2014). Cognitive content-specificity in anxiety and depressive disorder symptoms: a twin study of cross-sectional associations with anxiety sensitivity dimensions across development. *Psychological Medicine, 44*(16), 3469-3480.

Waszczuk, M. A., Zavos, H. M. S., Antonova, E., Haworth, C. M. A., Plomin, R., & Eley, T. C. (2015). A multivariate twin study of trait mindfulness, depressive symptoms and anxiety sensitivity. *Depression and Anxiety, 32*(4), 254-261.

Waszczuk, M. A., Brown, H. M., Eley, T. C., & Lester, K. J. (2015). Attentional control theory in childhood: enhanced attentional capture by non-emotional and emotional distractors in anxiety and depression. *PLoS ONE*, 10 (11), e0141535

OTHER PUBLICATIONS

Waszczuk, M. A., Zavos, H. M. S., & Eley, T. C. (2013). Genetic and Environmental Influences on Relationship between Anxiety Sensitivity and Anxiety Subscales in Children. *Journal of Anxiety Disorders, 27*(5), 475-484.

Krebs, G., **Waszczuk, M. A.**, Zavos, H. M. S., Bolton, D., & Eley, T. C. (2014). Genetic and environmental influences on obsessive-compulsive behaviour across development: a longitudinal twin study. *Psychological Medicine, 45*(7), 1539-1549.

Kanso, R., Hewstone, M., Hawkins, E., **Waszczuk, M. A.**, & Nobre, A. C. (2014). Power corrupts co-operation: cognitive and motivational effects in a double EEG paradigm. *Social Cognitive and Affective Neuroscience, 9*(2), 218-224.

de Gardelle, V., **Waszczuk, M. A.**, Egner, T., & Summerfield, C. (2013). Concurrent repetition enhancement and suppression responses in extrastriate visual cortex. *Cerebral Cortex, 23*(9), 2235-2244.

Hannigan, L. J., Walaker, N., **Waszczuk, M. A.**, McAdams, T. A., Eley, T. C. (In Press). Aetiological influences on stability and change in emotional and behavioural problems across development: a systematic review. *Psychopathology Review*.

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Waszczuk, M. A., Coulson, A., Gregory, A. M., & Eley, T. C. (In Sub). A longitudinal twin and sibling study of the hopelessness theory of depression in adolescence and emerging adulthood.

1. BACKGROUND

1.1. INTRODUCTION

Depression and anxiety are among the most common mental health problems in general population (Kessler, Berglund, et al., 2005). They are also among the most co-occurring psychiatric conditions, with comorbidity being the norm rather than the exception (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Kessler, Chiu, Demler, Merikangas, & Walters, 2005). Both depression and anxiety have their origins in childhood and adolescence (Costello et al., 2003; Ford, Goodman, & Meltzer, 2003), and are highly recurrent across development and adult life (Carballo et al., 2011; Ferdinand, Dieleman, Ormel, & Verhulst, 2007; Lahey, Zald, Hakes, Krueger, & Rathouz, 2014). They are associated with a range of negative outcomes, affecting family and peer relationships, education, employment, physical health and mortality (Clarke & Currie, 2009; Lerner et al., 2004; Owens, Stevenson, Hadwin, & Norgate, 2012). Comorbid depression and anxiety are associated with a higher burden than either condition alone (Moffitt et al., 2007). In order to inform treatment and prevention approaches, depression and anxiety need to be investigated together, with the aim to enhance our understanding of transdiagnostic and disorder-specific risk factors.

The relationship between depression and anxiety can be explored from multiple perspectives. The current thesis uses three approaches: genetically informative, longitudinal and experimental, to investigate two important aspects of this association. First, it focuses on the shared aetiology (defined in this thesis as genetic and environmental contributions to the trait or the relationship between traits) of depression and anxiety across development. Research in this field has moved on from simply estimating the genetic and environmental overlap between these conditions to considering more complex issues. These include differential relationship between depression and multiple anxiety types, such as the generalized anxiety,

panic or phobias; the age differences in the aetiological relationship between depression and these different anxiety types; as well as the role of stable and time-specific genetic and environmental influences in the continuity and co-occurrence of depression and different anxiety types across development. The second approach concerns the role of cognitive vulnerabilities in the development of both depression and anxiety. To date many studies have shown that a number of cognitive biases (Hadwin & Field, 2010; Mathews & MacLeod, 2005; Muris & Field, 2008) and cognitive deficits (Eysenck & Derakshan, 2011; Snyder, 2013) are associated with internalizing problems. These cognitive factors are relevant for psychological therapies commonly used to treat depression and anxiety, such as cognitive behavioural therapy (CBT). However, there are many outstanding questions, including the specificity of cognitive biases to depression and anxiety across development, the aetiology of these associations in younger people, and the relationship between cognitive deficits and cognitive biases.

The aim of this chapter is to provide a theoretical background for research into the role of genetic, environmental and cognitive factors in the co-occurrence of depression and anxiety. The thesis takes quantitative genetics approach to disentangling genetic and environmental influences in intergenerational transmission of comorbid psychopathology as its core theoretical framework. The chapter begins by describing the epidemiology and aetiology of depression and different anxiety disorders separately. Next, the comorbidity between depression and anxiety is discussed with relation to the epidemiology, treatment, theoretical models and aetiology of this relationship. The subsequent section concerns the role of cognitive biases in depression and anxiety, with a specific focus on anxiety sensitivity and the aetiological factors relevant to biased cognition. Next, cognitive deficits in depression and anxiety are discussed, with an emphasis on the role of executive functions and mindfulness in internalizing problems. Finally, the main aims of the current thesis are outlined.

1.2. DEPRESSION

This section discusses the epidemiology and aetiology of depression. First, clinical definition of depression is outlined, followed by prevalence rates, evidence for stability over time and impairment associated with this disorder. Second, genetic and environmental influences on depression are discussed, focusing on the aetiological effects within time as well as across time.

1.2.1. EPIDEMIOLOGY

Definition

It is normal to experience periods of sadness, for example in response to negative experiences such as bereavement, however in some individuals the low mood will persist, intensify and become pathological. Depression is defined in DSM-5 by the presence of five or more significantly distressing and impairing symptoms occurring during the same two week period, out of which at least one needs to be either depressed moor or loss of interest or pleasure (American Psychiatric Association, 2013). Other psychological and cognitive symptoms are feelings of worthlessness, inappropriate guilt, thoughts of suicide and diminished ability to think or concentrate. Other symptoms of depression are more physical and include change in weight and appetite, sleep disturbances such as insomnia or hypersomnia, as well as psychomotor agitation and fatigue. These are generally assessed by diagnostic interviews conducted by clinicians. In addition to depressive *disorder*, subthreshold depression *symptoms* that are conceptualised as dimensional are also of great interest to clinicians and researchers

(Balázs et al., 2013; Fergusson, Horwood, Ridder, & Beautrais, 2005; Pickles et al., 2001). Depression symptoms are generally captured by self-report questionnaires.

Prevalence

Depression is one of the most common psychiatric conditions. It is relatively rare in childhood, with prevalence estimates under 1% before the age of 10 (Ford et al., 2003). The prevalence rates of depression increase markedly in adolescence (Costello, Erkanli, & Angold, 2006; Ford et al., 2003; Moffitt et al., 2007), with prevalence in childhood estimated at 2.8% and in adolescence at 5.7% in a comprehensive meta-analytic study (Costello et al., 2006). This suggests that adolescence is a key developmental period for mood problems. Reasons for this developmental shift may include a range of biological and social changes, such as puberty and brain and cognitive maturation (Thapar, Collishaw, Pine, & Thapar, 2012). Depression remains highly prevalent in adulthood (12 month estimate of 9.5%) (Kessler, Chiu, et al., 2005), with about half of all the depression cases emerging before the age of 30 (Kessler, Berglund, et al., 2005). The lifetime prevalence of depression or any other mood disorder is 20.8%, affecting about one in five Americans at some point in their life (Kessler, Berglund, et al., 2005). The prevalence of subthreshold depression is thought to be even higher (Fergusson et al., 2005). There is converging evidence that depression is more common in females than in males (Hyde, Mezulis, & Abramson, 2008; Kessler, Berglund, et al., 2005) and that these sex differences emerge post-adolescence (Costello et al., 2006; Moffitt et al., 2007).

Stability

Depression is highly recurrent and shows considerable stability over time (often called *homotypic continuity*) (Carballo et al., 2011; Costello et al., 2003; Harrington, Fudge, Rutter, Pickles, & Hill, 1990; Lahey et al., 2014). In childhood and adolescence, a previous depression episode increases the likelihood of a future depression episode sevenfold, and the odds ratios remain high even when controlling for other comorbidities (odds ratio 4.2) (Costello et al.,

2003). Adolescent-onset depression is a significant predictor of depression in adulthood (Dunn & Goodyer, 2006; Harrington et al., 1990). However, some studies find that childhood-onset depression does not predict later mood problems, suggesting that depression pre- and post-puberty might be qualitatively different (Rutter, Kim-Cohen, & Maughan, 2006). Mood disorders remain stable in adulthood, with depression diagnosis moderately correlated (r=.36) with subsequent depression diagnosis three years later, when controlling for comorbidities (Lahey et al., 2014).

Impairment

Given the severity of depression symptoms and their chronic nature, it is not surprising that depression is associated with a range of impairments. First, a recent meta-analysis found that depression predicts poorer academic achievement (Riglin, Petrides, Frederickson, & Rice, 2014), while in adults depression is linked to reduced employment rates and productivity (Kessler & Frank, 1997; Lerner et al., 2004; Plaisier et al., 2010). Second, depression can have an adverse effect on psychosocial functioning and family relationships (Katon et al., 2010; Puig-Antich et al., 1993). It is also linked to a wide range of physical health problems, and multiple meta-analyses have found that depression associated with conditions such as heart disease, stroke, diabetes and asthma (Clarke & Currie, 2009). This might in part be due to the adverse behavioural changes associated with depression. For example, depressed youths are more likely to engage in substance use and are less physically active (Brown, Lewinsohn, Seeley, & Wagner, 1996; Katon et al., 2010). Depression is also thought to interfere with the treatment of, and recovery from, physical disorders (Clarke & Currie, 2009). It is also strongly associated with an increase in the suicide attempts and risk (Harris & Barraclough, 1997). Finally, from the societal perspective, depression carries a significant economic burden, as it is estimated that it will cost the UK £3 billion in health services care and £12.2 billion in lost employment by 2026 (McCrone, Dhanasiri, Patel, Knapp, & Lawton-Smith, 2008). Taken together, depression constitutes a multifaceted risk factor to individual's development and wellbeing.

1.2.2. AETIOLOGY

Twin methodology

Genetically informative approaches are able to estimate the relative influence of latent genetic and environmental factors, as well as their interplay, in the aetiology of psychiatric traits (Plomin, DeFries, Knopik, & Neiderhiser, 2013). Four types of aetiological influences can be estimated. *Additive genetic influences* (A) capture the cumulative effect of alleles or genetic loci on a trait, representing the genetic component of variance responsible for family resemblance. *Dominant genetic influences* (D) estimate the interactions between genes at a specific locus and across different loci (epistasis), but are rarely seen in twin studies of internalizing problems. *Shared environmental influences* (C) reflect environmental influences common to family members that make them resemble one another. *Non-shared environmental influences* (E) reflect individual-specific environmental influences that make the family members different from one another. It is important to highlight that the estimates reflect latent, rather than measured aetiological effects. For discussion of different theoretical models of intergenerational transmission see section 1.4.4. In short, *family studies* look at the aggregation of disorders and symptoms in the families, providing information on familial (combined genetic and shared environmental) and non-shared environmental influences on these traits. *Twin studies* are able to disentangle the magnitude of the genetic and shared environmental influences on a single trait, or shared between two or more traits, by comparing within-pair similarly between monozygotic (MZ) and dizygotic (DZ) twins. Twin methodology is described in more detail in section 2.4.

Univariate influences

Studies investigating aetiology of depression have found that it aggregates in families (Rice, Harold, & Thapar, 2002b; Shih, Belmonte, & Zandi, 2004; Sullivan, Neale, & Kendler, 2000),

indicating the significant familial influences. Multiple meta-analyses of twin studies strongly suggest that depression is moderately heritable in childhood as well as in adulthood, with the remaining variance explained by environmental influences (Franic, Middeldorp, Dolan, Ligthart, & Boomsma, 2010; Rice et al., 2002b; Shih et al., 2004; Sullivan et al., 2000; Thapar & Rice, 2006). In children, there are both shared and non-shared environmental influences on depression (Burt, 2009). The shared environmental influences decrease while heritability increases across development (Bergen, Gardner, & Kendler, 2007; Rice, Harold, & Thapar, 2002a), and in adults only the non-shared environmental influences are observed alongside genetic influences. One of the reasons why heritability increases in adolescence might be due to an increase in behaviour-dependent negative life events (Rice, Harold, & Thapar, 2003). It remains debated whether there are sex differences in the aetiology of depression, with some studies finding different heritability estimates in males and females (Happonen et al., 2002; Rice et al., 2002a), while others finding no such sex differences (Boomsma, Van Beijsterveldt, Hudziak, & Van Beijsterveldt, 2005; Burt, 2009).

Longitudinal influences

Recently twin studies have begun investigating developmental patterns of genetic and environmental effects in longitudinal study designs, in order to see how these influences operate over time (Ronald, 2011). Longitudinal twin studies can estimate both the genetic and environmental *stability* (the degree to which aetiological influences contribute to the continuity of the symptoms), *innovation* (the degree to which new aetiological influences emerge over time and contribute to the change of symptoms) and *attenuation* (the degree to which previous aetiological influences decline over time) (Kendler, Gardner, Annas, et al., 2008). Twin studies find support for genetic stability in depression across development as well as in adulthood (Bolhuis et al., 2014; Gillespie et al., 2004; Lau & Eley, 2006; Nivard et al., 2014; Tully, Iacono, & McGue, 2010). However, one study found substantial contribution of shared environmental influences to the stability of depression in children and adolescents (Scourfield

et al., 2003). Furthermore, some studies find evidence for genetic innovation and attenuation in young people (Lau & Eley, 2006; Nivard et al., 2014; Scourfield et al., 2003), suggesting that genetic influences may drive change in depression symptoms. Finally, the majority of the studies have found that the non-shared environmental factors are time-specific and contribute to change of depression symptoms over time. One notable exception is a study by O'Connor, Neiderhiser, Reiss, Hetherington, and Plomin (1998) who found that the non-shared environmental influences accounted for about half the continuity of depression from middle childhood to late adolescence. Taken together, these studies suggest that latent genetic influences largely contribute to the stability of depression while non-shared environmental influences tend to contribute to change in symptoms over time. Furthermore, results suggest that genetic innovation and attenuation can be observed in young people, indicating that the aetiology of depression symptoms might be more dynamic in childhood and adolescence than in adulthood. The genetic and environmental influences on the stability and change of depression symptoms across adolescence and young adulthood are explored in chapter 4.

1.2.3. SUMMARY

Depression is a highly prevalent psychiatric condition that tends to emerge in adolescence and young adulthood. It is a recurrent disorder and symptoms tend to continue across development and adulthood. Depression constitutes a significant psychosocial and educational impairment, as well as causes a considerable burden on the individual as well as the society. Focusing on the aetiology of depression, genetically informative studies reveal that it is moderately heritable, with the remaining variance explained by environmental influences. Shared environmental influences are evident in childhood, but play a diminishing role in adolescence and adulthood. Stable latent genetic influences are thought to largely contribute to the continuity of depression over time, although there is evidence for genetic innovation

and attenuation in childhood and adolescence. Shared environmental influences may also contribute to the stability of depression across development, while non-shared environmental influences are largely time-specific and are thought to largely contribute to the change over time.

1.3. ANXIETY

This section focuses on the current knowledge of epidemiology and aetiology of anxiety. First, clinical definitions of anxiety disorders relevant to this thesis are outlined. Next, prevalence rates, evidence for continuity within and across diagnostic borders, and impairment associated with these anxiety disorders is discussed. Second, the evidence for genetic and environmental influences on different anxiety types, and their aetiological overlap, is presented. Finally, longitudinal genetic and environmental influences on anxiety are considered.

1.3.1. EPIDEMIOLOGY

Definitions

Anxiety is an adaptive emotion that evolved to increase chances of survival in threatening circumstances (Marks & Nesse, 1994). It is normally experienced by children as they develop, however, in some individuals, fear and anxiety persist, intensify and become pathological. Anxiety is not a unified condition. Instead, it is broadly used to bring together specific disorders, such as generalised anxiety disorder, panic disorder and phobias that are characterised by excessive, persistent and impairing worry or fear (American Psychiatric Association, 2013). All of these different anxiety disorders are characterised by a range of cognitive, physical and behavioural symptoms. *Generalized anxiety disorder* is defined in the

DSM-5 by the presence of excessive and uncontrollable worry about more than one issue during majority of the days for over 6 months period. Worry must be accompanied by at least three of the following significantly distressing and impairing symptoms: irritability, difficulty concentrating, restlessness, muscle tension, fatigue and sleep disturbances. *Panic disorder* is characterized by the occurrence of panic attacks, which must be accompanied by at least one month of subsequent worry about having another panic attack or its consequences, as well as by the significant maladaptive behavioural changes related to the attack. *Separation anxiety* is defined in the DSM-5 by meeting at least three criteria that centre on the distressing and impairing fears and worries about the separation from home or major attachment figure, behavioural reluctance to separate from these figures, and physical symptoms such as nausea when the separation occurs or is anticipated. One of the notable updates introduced by the DSM-5 was to remove separation anxiety from the category of disorders usually diagnosed in young people and broadening of the diagnostic criteria to allow for adult-appropriate symptoms. In people younger than 18 years separation anxiety symptoms need to persist for at least 1 month, while in adults the required duration is at least 6 months. S*ocial anxiety* disorder is defined in the DSM-5 by significantly impairing fears and excessively avoidant behaviours specific to social settings, that persist for over 6 months. Some of the symptoms of social anxiety include fear of social rejection or performing in front of others. Finally, *specific phobia* is characterised by persistent, excessive and consistently observed fear and avoidance behaviours that are cued by the presence or anticipation of a specific object or situation. Types of specific phobia include fears of animals (e.g. spiders), natural environments (e.g. heights) and situations (e.g. enclosed places). Anxiety disorders are generally assessed by diagnostic interviews conducted by clinicians. In addition to anxiety *disorder*s that meet the diagnostic criteria, dimensional subthreshold anxiety *symptoms* are also of interest to clinicians and researchers (Balázs et al., 2013; Fergusson et al., 2005; Pickles et al., 2001). Anxiety symptoms are generally captured by self-report questionnaires.

Prevalence rates

Anxiety is a common psychiatric condition in childhood, with prevalence estimates of 3.2% in 5-7 year olds, with the most prevalent types of anxiety in this age group being separation anxiety disorder (1.5%) and social phobia (1.1%) (Cartwright-Hatton, McNicol, & Doubleday, 2006; Ford et al., 2003). These prevalence estimates increase to 5% in mid-adolescence. About half of all anxiety disorders emerge before the age of 11 years (Kessler, Berglund, et al., 2005), making childhood a crucial developmental period for anxiety. The estimates differ by anxiety type, for example almost all cases of separation anxiety and phobias emerge before adulthood, while only about a quarter of all the generalized anxiety and panic cases emerge before adulthood. Anxiety remains the most highly prevalent mental disorder in adulthood (12 month estimate of 18.1%) (Kessler, Chiu, et al., 2005). The lifetime prevalence of any anxiety disorder is 28.8%, affecting about one in three Americans (Kessler, Berglund, et al., 2005). Notably the estimates of lifetime prevalence differ by anxiety type, being 5.7% for generalized anxiety disorder, 4.7% for panic disorder, 5.2% for separation anxiety and 12.1-12.5% for phobias. There is converging evidence that anxiety is more common in females than in males (Kessler, Berglund, et al., 2005) and that these sex differences may emerge only post-adolescence (Ford et al., 2003), although some studies do find that anxiety disorders are more common in adolescent girls than boys (Lewinsohn, Gotlib, Lewinsohn, Seeley, & Allen, 1998).

Stability

Anxiety is highly recurrent and shows considerable continuity across the lifespan, both within the same anxiety disorder (*homotypic continuity*) as well as across different anxiety disorders, with one anxiety disorder predicting another type of anxiety disorder (*heterotypic continuity*) (Costello et al., 2003; Lahey et al., 2014). In childhood and adolescence, previous anxiety increases the likelihood of future anxiety over twofold, and the odds ratios remain high even when controlling for other comorbidities (odds ratio 2.0) (Costello et al., 2003). Individuals diagnosed with anxiety disorder in childhood are likely to experience anxiety later in

adolescence (Ferdinand et al., 2007), with the homotypic continuity higher than heterotypic continuity. Anxiety early in life is a significant predictor of adult anxiety disorders (Bittner et al., 2007; Pine, Cohen, Gurley, Brook, & Ma, 1998), with most adult cases receiving an anxiety diagnosis before the age of 15 years (Gregory et al., 2007). Homotypic continuity remains significant in adulthood, with an anxiety diagnosis moderately correlated with the subsequent anxiety diagnosis three years later (r=.27 for generalized anxiety, r=.42 for agoraphobia and/or panic disorder, r=.43 for social phobia and r=.35 for specific phobia), when controlling for comorbidities (Lahey et al., 2014). Heterotypic continuity between the different anxiety disorders was generally smaller but also significant (r=.10-.19).

Impairment

The pervasive and chronic nature of anxiety contributes to the substantial impairments associated with this condition. Anxiety disorders have a negative impact on child and adolescent development, disturbing well-being, as well as interfering with academic performance and impairing interpersonal interactions (Essau, Conradt, & Petermann, 2000; Langley, Bergman, McCracken, & Piacentini, 2004; Owens et al., 2012; Van Ameringen, Mancini, & Farvolden, 2003). In adults anxiety has a detrimental effect on employment (Plaisier et al., 2010; Waghorn, Chant, White, & Whiteford, 2005), for example by increasing absenteeism and hindering career trajectories. Anxiety is also thought to be a risk factor for several physical disorders, such as respiratory symptoms (Clarke & Currie, 2009; Kotov et al., 2015; Litcher-Kelly et al., 2014), and is associated with unhealthy behaviours such as substance use (Grant et al., 2004; Woodward & Fergusson, 2001). Finally, anxiety carries a significant economic burden on modern societies, for example it is estimated that it will cost the UK £2 billion in health services care and £12.2 billion in lost employment by 2026 (McCrone et al., 2008).

1.3.2. AETIOLOGY

Univariate influences

Studies investigating the aetiology of anxiety have found that it aggregates in families (Beidel & Turner, 1997; Eley, Collier, McGuffin, Owen, & Gottesman, 2002; Hettema, Neale, & Kendler, 2001), suggesting significant familial influences on this condition. A wealth of evidence from twin studies indicates moderate genetic contribution to anxiety in childhood and across the lifespan, with environmental influences also found to be significant, implying a complex aetiology (Burt, 2009; Franic et al., 2010; Gregory & Eley, 2009; Hettema et al., 2001; Shimada-Sugimoto, Otowa, & Hettema, 2015). Meta-analyses do not find sex differences in the aetiology of anxiety and the heritability estimates are thought to increase over time (Bergen et al., 2007; Burt, 2009). Many studies investigated heritability of anxiety as a total scale. However, the magnitude of genetic and environmental influences can also be investigated across different anxiety symptom clusters. *Generalized anxiety* in children and adolescents is moderately to highly heritable, with the remaining variance explained by the non-shared environmental influences (Ogliari et al., 2006; Waszczuk, Zavos, & Eley, 2013). Comparable estimates have been found in adults (Hettema et al., 2001; Kendler, Neale, Kessler, Heath, & Eaves, 1992a). Similarly, *panic* symptoms have been found to be moderately heritable in children (Eley, Gregory, Clark, & Ehlers, 2007) and in adults (Chantarujikapong et al., 2001; Hettema et al., 2001; Schumacher et al., 2011). *Separation anxiety* is also influenced by a combination of genetic and non-shared environmental factors, but the evidence suggests that shared environmental influences might also be significant in childhood (Eley et al., 2003; Silberg, Rutter, & Eaves, 2001). For example, Eley et al. (2003) found comparable moderate genetic and shared environmental influences on separation anxiety in 4 year old children. This has been confirmed in a recent meta-analysis of 18 twin studies (Scaini, Ogliari, Eley, Zavos, & Battaglia, 2012). Another meta-analysis of 13 cohorts found that *social anxiety* is moderately

heritable, with large non-shared environmental influences, indicating that idiosyncratic experiences such as difficulties with peers might be important in the aetiology of this disorder (Scaini, Belotti, & Ogliari, 2014). The study has found significantly higher heritability of social anxiety in children than in adults, and the heritability was higher when social anxiety was measured as dimensional symptoms rather than using clinical diagnosis. Finally, another recent meta-analysis of 15 studies in adults confirmed that *fears and specific phobias* are moderately influenced by genetic factors (Van Houtem et al., 2013). Animal and blood-injury-injections phobias were most highly heritable, and there were no shared environmental influences on any of the specific phobias. These results are in line with findings from child samples, for example specific phobias in 6 year old children have been shown to be moderately heritable, with the remaining variance explained by both shared and non-shared environmental influences (Eley, Rijsdijk, Perrin, O'Connor, & Bolton, 2008). In sum, these studies suggest that both genetic and environmental vulnerabilities are important in anxiety disorders, but that the relative influence of each on individual anxiety subscales may differ, some being more heritable and some more under environmental influences.

Multivariate influences

Multivariate behavioural-genetic analyses can be used to explore genetic and environmental influences underlying the co-occurrence of different anxiety types. A recent study found that common genetic factors explained a substantial amount of covariance between generalized anxiety, panic, separation and social anxiety symptoms in young people, with non-shared environmental influences contributing very little to the co-morbidity (Ogliari et al., 2010). Other studies have also found genetic overlap between a range of anxiety disorders, such as overanxious disorder, general distress, separation and social anxiety and specific phobias in childhood and adolescence (Eley et al., 2003; Eley, Rijsdijk, et al., 2008; Hallett, Ronald, Rijsdijk, & Eley, 2009; Silberg et al., 2001). Moreover, these studies have also found a common shared environmental factor that influences the co-occurrence of the different anxiety types in young

people. The genetic (but not the shared environmental) overlap between the different types of anxiety has also been identified in adult studies (Czajkowski, Kendler, Tambs, Røysamb, & Reichborn-Kjennerud, 2011; Hettema, Prescott, Myers, Neale, & Kendler, 2005). In sum, research suggests that familial influences underpin the co-morbidity between the different anxiety types, with the non-shared environmental influences being disorder-specific. Multivariate results support the *generalist genes hypothesis* (Eley, 1997; Plomin & Kovas, 2005), which proposes that traits co-vary due to shared genetic influences, while non-shared environmental influences are generally symptom-specific and contribute to the differentiation between the disorders.

Influences on homotypic continuity

Eight twin studies to date have investigated the relative contribution of the genetic and environmental influences to the homotypic continuity and change of anxiety symptoms. All studies found that latent genetic influences contribute substantially to the stability of total anxiety scores and the fears/specific phobias, across development as well as in adulthood (Garcia et al., 2013; Gillespie et al., 2004; Kendler, Gardner, Annas, et al., 2008; Lewis & Plomin, 2015; Nivard et al., 2014; Trzaskowski, Zavos, Haworth, Plomin, & Eley, 2011; Waszczuk et al., 2013; Zavos, Rijsdijk, & Eley, 2012). However, three of these studies also found evidence for genetic innovation and attenuation alongside genetic stability (Kendler, Gardner, Annas, et al., 2008; Lewis & Plomin, 2015; Trzaskowski et al., 2011), suggesting that genetic influences contribute to changes in anxiety symptoms across childhood and adolescence. Shared environmental influences were also found to contribute to the stability of phobias in young people (Kendler, Gardner, Annas, et al., 2008; Trzaskowski et al., 2011). Unlike the stable genetic and non-shared environmental effects, the non-shared environmental influences were largely time-specific and contributed to change in symptoms over time, possibly because non-shared environmental experiences such as stressful life events are transient. One of the reasons for mixed results regarding genetic innovation across

development might be that despite the heterogeneity of anxiety disorders, most relevant studies have used a total anxiety score. Only two studies to date have investigated the etiology of homotypic continuity of specific subtypes of anxiety symptoms. Kendler, Gardner, Annas, et al. (2008) examined three types of phobia from childhood to adulthood, and found more stable shared environmental influences on animal than situational and blood/injury fears. Waszczuk et al. (2013) investigated genetic and environmental influences on panic, separation and generalized anxiety symptoms across middle childhood, and found genetic stability and largely time-specific environmental influences consistently in the three syndromes. The contribution of genetic and environmental influences to the homotypic continuity and change of a range of anxiety symptom clusters, such as generalized anxiety, panic, separation and social anxiety is investigated in chapter 4.

Influences on heterotypic continuity

Finally, to date only two twin studies have investigated the role of genetic and environmental influences in the *heterotypic continuity* between different anxiety types (Roberson-Nay, Eaves, Hettema, Kendler, & Silberg, 2012; Silberg et al., 2001). Silberg et al. (2001) found that the heterotypic continuity between three types of anxiety (overanxious disorder, separation anxiety and specific phobia) in childhood and adolescence was driven by genetic and shared environmental influences. Roberson-Nay et al. (2012) found that the genetic influences on childhood separation anxiety disorder continue to influence adult onset panic attacks However, the aetiology of heterotypic continuity between other types of anxiety across development remains largely unknown (addressed in chapter 4).

1.3.3. SUMMARY

Anxiety disorders are very common psychiatric conditions that tend to emerge early in childhood. Anxiety is chronic and continues into adolescence and adulthood both within and across the diagnostic types. It is associated with a wide range of functional impairments and carries a substantial health burden on the individual as well as society. Focusing on the aetiology of anxiety, genetically informative studies reveal that all anxiety types are moderately heritable, with the remaining variance explained by environmental influences. There are important age differences in the aetiology of anxiety, with heritability estimates thought to increase over time. Furthermore, in young people shared environmental influences are thought to be substantial for separation anxiety and phobias. Most of the genetic and shared environmental influences are also common to different anxiety types, underpinning their co-occurrence, while the non-shared environmental influences are generally symptom-specific and contribute to the differentiation between the disorders. Stable latent genetic influences largely contribute to the continuity of anxiety over time, although there is evidence for genetic innovation and attenuation across development, indicating that age-specific genetic changes can alter the course of anxiety symptoms. Shared environmental influences are thought to contribute to the stability of fears and specific phobias across development. Non-shared environmental influences are largely time-specific and are thought to contribute to change over time.

1.4. COMORBIDITY OF DEPRESSION AND ANXIETY

This section focuses on the comorbidity of depression and anxiety. First, the evidence for the co-occurrence between these two disorders, both within and across time, is discussed. Second,

the impairment associated with comorbid internalizing problems is outlined in the context of implications of this comorbidity for treatment strategies. Third, several influential theoretical models proposed to explain the relationship between depression and different anxiety types are outlined. Finally, the evidence for common genetic and environmental influences on depression and anxiety is presented.

1.4.1. EPIDEMIOLOGY

Conceptual considerations

Comorbidity is defined as the co-occurrence of two supposedly separate conditions at above chance levels (Rutter, 1994). Depression and anxiety frequently co-occur within time (*concurrent comorbidity*), and across the life span (*successive comorbidity*). The substantial associations between depression and all anxiety types have been extensively reviewed and have been found across both clinical and community samples, across studies that use different informants, and across the full range of definitions of both *symptoms* and *diagnoses* of depression and anxiety (Angold, Costello, & Erkanli, 1999; Beesdo, Knappe, & Pine, 2009; Brady & Kendall, 1992; Costello et al., 2003; Cummings, Caporino, & Kendall, 2014; Kessler, Chiu, et al., 2005; Lahey et al., 2014). Prior to discussing this comorbidity in more detail, it is important to highlight some of the methodological issues relevant to the co-occurrence of internalizing disorders. First, depression and anxiety are characterised by somewhat overlapping diagnostic criteria, especially when looking at generalized anxiety. These include fatigue, difficulty concentrating, sleep problems and irritability. The overlap suggests that comorbidity may be an artefact of the current diagnostic system, and this issue is discussed in more detail in section 1.4.3. Second, many questionnaire measures use similar or overlapping items to assess depression and anxiety symptoms, which may inflate the estimates of the co-

occurrence of these problems. However, studies that investigated this issue directly have found that controlling for the overlap and for the shared method variance in general does not markedly reduce the association between depression and anxiety (Cole, Truglio, & Peeke, 1997; Stark & Laurent, 2001).

Aside from these methodological explanations, there are several theoretical reasons for the presence of comorbid psychopathology (Angold et al., 1999; Rutter, 1997). First, anxiety and depression may be manifestations of the same disorder, either occurring concurrently or successively as two stages of the same psychopathology, with anxiety turning into depression, or conversely depression leading to anxiety. Second, the comorbidity may arise as an artefact of the same or correlated risk factors. As there are many influences on anxiety and depression, and many risk factors such as family adversity might be central to both disorders. Third, comorbid conditions may be distinct from the conditions that occur alone, for example panic disorder is classified separately when it co-occurs with agoraphobia. Finally, one condition may predispose individuals to another condition, for example risk factors and pathways that predispose individuals to one disorder are often associated with risk factors and pathways that predispose individuals to another disorder. The risk pathways might include various processes, including cognitive patterns discussed in more detail in section 1.5. The evidence and associated theoretical models that closely relate to these different explanations of comorbidity are discussed in this section.

Concurrent comorbidity

Looking at concurrent comorbidity, a meta-analysis of studies in the community samples has found that in children and adolescents with a primary diagnosis of depression, anxiety disorders are the most common comorbid mental health problem, with the comorbidity rates ranging approximately 20%-75% (Angold et al., 1999). In clinical samples, comorbidity rates of up to 80% have been found (Birmaher, Ryan, Williamson, Brent, & Kaufman, 1996). Another study has estimated that 59% of adults with a lifetime diagnosis of depression also meet

criteria for a lifetime diagnosis of anxiety (Kessler et al., 2003). Conversely, somewhat fewer (approximately 5-55%) youths with a primary anxiety disorder were found to receive a comorbid depression diagnosis (Angold et al., 1999; Axelson & Birmaher, 2001). This asymmetry in the rates of comorbidity in individuals with the primary anxiety versus depression diagnosis might be because the mean age of onset of anxiety precedes that of depression (Beesdo et al., 2009; Kessler, Chiu, et al., 2005; Wittchen, Kessler, Pfister, & Lieb, 2000). There are also important differences in the comorbidity between depression and different anxiety types. For example, 20% of individuals diagnosed with a lifetime social phobia meet lifetime criteria for a depression (Merikangas & Angst, 1995), as compared to over half of individuals with a lifetime diagnosis of panic attacks and panic disorder also meeting the lifetime depression diagnoses (Kessler et al., 1998). Generalized anxiety is particularly highly comorbid with depression, with some clinicians questioning whether the two disorders can be reliably differentiated (Hettema, 2008a; Mennin, Heimberg, Fresco, & Ritter, 2008; Moffitt et al., 2007).

Successive comorbidity

With regards to successive comorbidity, many studies have found that anxiety precedes and might be a risk factor for developing depression in the future (Avenevoli, Stolar, Li, Dierker, & Merikangas, 2001; Cole, Peeke, Martin, Truglio, & Seroczynski, 1998; Wittchen et al., 2000). In support of this view, daily anxious mood has also been found to temporally precede and predict daily depressed mood at a two-day lag, but not vice versa (Starr & Davila, 2012). This suggests that anxiety might have depressogenic effects through a variety of mechanisms, such as anxiety-driven social withdrawal and avoidance of expressing emotions (Gazelle & Ladd, 2003; Grant, Gayle Beck, Farrow, & Davila, 2007).

However, the directionality of successive comorbidity is still debated and many studies have found that the reverse pattern occurs equally often, with depression being a risk factor for future anxiety (Costello et al., 2003; Pine et al., 1998; Zavos, Rijsdijk, et al., 2012), especially for

panic disorder (Kessler et al., 1998). One mechanisms that may explain why earlier depression may lead to subsequent anxiety is avoidance. Behavioural and cognitive (experiential) avoidance is central to all anxiety types, as it maintains and escalates learned fears by validating the escape from feared thoughts, objects or places as a coping mechanism in patients (Borkovec, Alcaine, & Behar, 2004; Hofmann, 2007). Avoidance is a key therapeutic treatment target for anxiety, with approaches such as exposure therapy aiming to overcome avoidance through gradual habitation and creation of new associations with feared objects (Feske & Chambless, 1995; Parsons & Rizzo, 2008). Importantly, earlier depression may considerably contribute to avoidance due to low motivation, hopelessness and inactivity, resulting in triggering anxiety and making it more difficult to treat anxiety symptoms through therapy.

Finally, there is also evidence that a reciprocal relationship between depression and anxiety is established as early as in adolescence (Costello et al., 2003; Lahey et al., 2014; Moffitt et al., 2007). For example, Costello et al. (2003) found that in childhood and adolescence, previous anxiety increases the likelihood of future depression threefold, while previous depression increases the likelihood of future anxiety almost sixfold.

1.4.2. TREATMENT

Impairment associated with comorbidity

Comorbid depression and anxiety is associated with greater health burden than either condition alone. Children and adolescents with comorbid depression and anxiety are more impaired than individuals with a single diagnosis of anxiety, although not more than individuals diagnosed with depression alone (Cummings et al., 2014). The impairments associated with comorbid depression in youths with principal anxiety diagnosis include worse family

functioning and increased severity of depression and anxiety symptoms (O'Neil, Podell, Benjamin, & Kendall, 2010). Comorbidity of depression and anxiety in adolescence is also associated with a range of problems, such as the academic difficulties, mental health treatment utilization, suicide attempts, functioning and conflict with parents (Lewinsohn, Rohde, & Seeley, 1995). Comorbidity in adults is associated with more recurrent course, higher medication and mental health service use but poorer treatment response, and a greater suicide risk, than depression or anxiety alone (Moffitt et al., 2007).

Impact of comorbidity on treatment

Comorbidity of depression and anxiety has important implications for the treatment of these problems. Two lines of recommended treatment for depression and anxiety include psychological interventions, such as CBT or behavioural activation, and pharmacological treatment, such as selective serotonin reuptake inhibitors (SSRIs) (AACAP, 2007a, 2007b). Most of the available treatments have been developed to be disorder-specific and multiple diagnoses may complicate treatment planning. Comorbidity can interfere with disorder-specific *CBT* and reduce likelihood of recovery (Berman, Weems, Silverman, & Kurtines, 2000; Bruce et al., 2005; Curry et al., 2006; Young, Mufson, & Davies, 2006), but the findings are not consistent (Cummings & Fristad, 2012; Kley, Heinrichs, Bender, & Tuschen-Caffier, 2012; Pössel, Seemann, & Hautzinger, 2008; Rapee et al., 2013; Rohde, Clarke, Lewinsohn, Seeley, & Kaufman, 2001). Comorbidity has also been found to interfere with the disorder-specific *pharmacological* treatment in children and adults (Curry et al., 2006; Geller et al., 2003; Vitiello & Research Units on Pediatric Psychopharmacology Anxiety Study Group, 2003). However, other studies have found that comorbid anxiety is not associated with SSRI outcomes in depressed youths (Cheung et al., 2010; Tao et al., 2009). In sum, the findings are mixed, although there seems to be an indication in the literature that depression interferes with anxiety treatment more often than the reverse. This might be because depression is more resistant to treatment than anxiety (Chu & Harrison, 2007). Some studies suggest that

comorbid depression and anxiety in young people should be treated with a combination of CBT and antidepressant medication (Asarnow et al., 2009; March et al., 2004).

Transdiagnostic treatments

The commonalities between depression and anxiety can also be used to improve treatment approaches. Many studies find generalisation of the CBT and pharmacological treatment effects to comorbid disorders that were not a primary target of the intervention (Allen et al., 2010; Hilton et al., 2013; Hudson & Pope, 1990; Ollendick, Öst, Reuterskiöld, & Costa, 2010; Rapee et al., 2013; Weersing, Rozenman, Maher-Bridge, & Campo, 2012). For example, the CBT for panic disorder has been found to reduce the generalized anxiety and depression symptoms alongside the panic symptoms (Allen et al., 2010). Understanding why depression and anxiety co-occur may help to inform treatments that target transdiagnostic liability factors, resulting in simultaneous treatment of multiple disorders in a single protocol (Krueger & Eaton, 2015). The unified cognitive treatment approaches have recently been developed and have been found to be effective, as they target aspects of emotional processing and regulation of emotional experiences that are common to internalizing disorders (Barlow, Sauer-Zavala, Carl, Bullis, & Ellard, 2014; Farchione et al., 2012; McEvoy, Nathan, & Norton, 2009; Titov et al., 2011). However, it is also important to note that certain types of anxiety might require symptom-specific treatment, such as an exposure therapy in phobias that is tailored to the specific fears.

1.4.3. THEORETICAL MODELS

Categorisation in diagnostic manuals

Depression and different anxiety disorders are defined as distinct and independent conditions in the official nosologic systems such as DSM-5 (American Psychiatric Association, 2013) and

ICD-10 (World Health Organization, 1992). The evidence of substantial comorbidity between depression and anxiety (discussed in the section 1.4.1) suggests that the relationship between these disorders might not be fully captured by the diagnostic manuals. Furthermore, when conceptualised as fundamentally separate phenomena, depression and different anxiety disorders should be distinguished by the aetiological influences, risk factors, developmental course and the neurological, cognitive and behavioural profiles. Given that a valid classification system is crucial for reliable diagnostic assessment, research and intervention, multiple theoretical models of the relationship between depression and anxiety have been proposed to address the limitations of current nosologic systems.

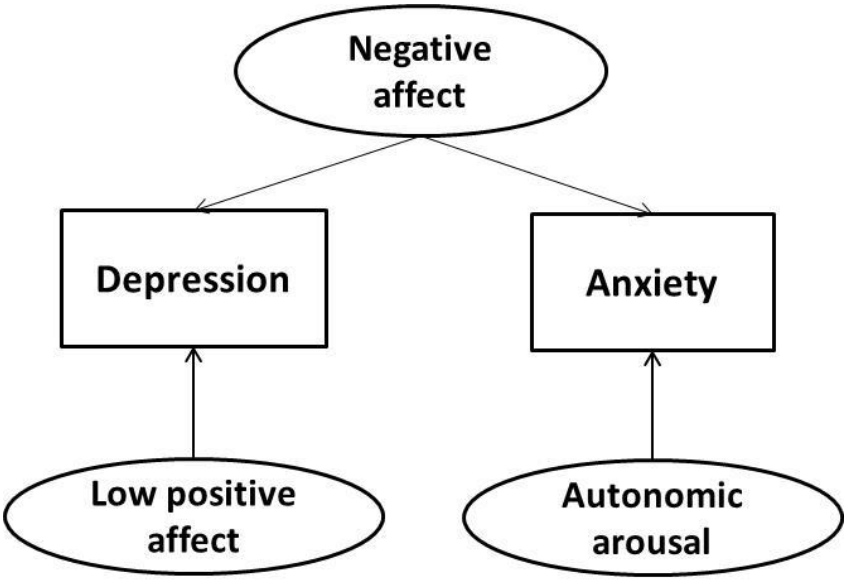
Bifactor models

Bifactor models, also known as general-specific models, are an analytic approach particularly well suited to testing the relationship between different multifaceted constructs (Chen, Hayes, Carver, Laurenceau, & Zhang, 2012; Chen, West, & Sousa, 2006). A bifactor model assumes that there is a general factor that accounts for the common variance shared by all the variables in the model, alongside variable-specific factors, each of which accounts for the unique variance of the specific variable over and above the general factor. Often several competing bifactor models can be fitted to the data to test which of different higher and lower order structures best describes the relationship between the variables. For example it can be investigated whether one or more general factors should be fitted, and which variables should load on each of the general factors, for example see Brodbeck, Abbott, Goodyer, and Croudace (2011). To aid model selection, models can be directly compared using a range of fit statistics, explained in more detail in section 2.4.4. Bifactor models have commonly been applied to understand the relationship between depression and anxiety.

Tripartite model

One of the best known theoretical models based on the bifactor general-specific approach that aimed to describe how depression and anxiety are related is *the tripartite model* (Clark & Watson, 1991) (Figure 1.1). The model has categorised depression and anxiety as separate disorders, but aimed to capture both their disorder-specific and shared characteristics. The model proposes that negative affect is common to both depression and anxiety, while autonomic arousal is specific to anxiety, and low positive affect is specific to depression. Several studies have demonstrated support for the tripartite model in adults (Watson et al., 1995a, 1995b) and in children and adolescents (Anderson & Hope, 2008; Cannon & Weems, 2006; Joiner, Catanzaro, & Laurent, 1996; Olino, Klein, Lewinsohn, Rohde, & Seeley, 2008; Tully, Zajac, & Venning, 2009). Thus, the empirical evidence suggests that depression and anxiety are characterised by the combination of shared and specific factors. However, some of the aspects of the tripartite model have been criticised. For example, some studies have found that autonomic arousal and low positive affect are not disorder-specific, but instead should be seen as factors common to depression and anxiety (Dieleman, Van der Ende, Verhulst, & Huizink, 2010; Greaves-Lord et al., 2007). It is also unclear whether the tripartite model applies in young children (Cole et al., 1997). Furthermore, one of the important limitations of the tripartite model is that it conceptualises anxiety as a homogenous disorder. Studies that examine multiple types of anxiety have found that the tripartite model might differ depending on the type of anxiety investigated. For example physiological arousal has been found to be only specific to panic disorder, while negative affect has been found to characterise social phobia as much as it does depression (Anderson, Veed, Inderbitzen-Nolan, & Hansen, 2010; Brown, Chorpita, & Barlow, 1998; Chorpita, 2002; Chorpita, Plummer, & Moffitt, 2000). In sum, the tripartite model has been central in highlighting the disorder-specific and common factors in depression and anxiety, and it has influenced the research into the nosology of internalizing disorder. However, the evidence suggests that the original model is not sufficient in describing the association between depression and all types of anxiety.

Figure 1.1 – The tripartite model of depression and anxiety



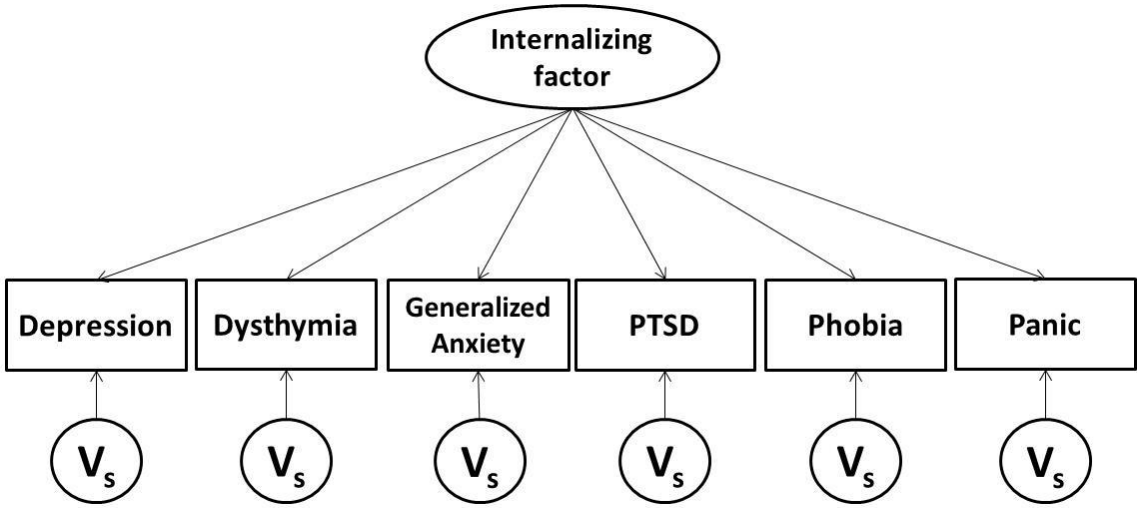
Note. The model is adapted from Clark and Watson (1991).

Higher order internalizing factor

The hierarchical model of depression and anxiety (Figure 1.2) was proposed to address the limitations of the tripartite model by integrating multiple anxiety types into the structure (Mineka, Watson, & Clark, 1998). The model once again specifies that each disorder is characterised by both shared and disorder-specific factors. Specifically, the hierarchical conceptualisation proposes that majority of variance in depression and anxiety is shared, and can be parsimoniously accounted for by a higher-order *internalizing factor*. The internalizing dimension has been supported in adults (Eaton, Krueger, & Oltmanns, 2011; Fergusson, Horwood, & Boden, 2006; Goldberg, Krueger, Andrews, & Hobbs, 2009; Krueger, Caspi, Moffitt, & Silva, 1998; Krueger & Finger, 2001; McGlinchey & Zimmerman, 2007; Røysamb et al., 2011; Seeley, Kosty, Farmer, & Lewinsohn, 2011; Simms, Prisciandaro, Krueger, & Goldberg, 2012; Simms, Grös, Watson, & O'Hara, 2008) as well as in young people (Gomez,

Vance, & Gomez, 2013; Prenoveau et al., 2010; Trosper, Whitton, Brown, & Pincus, 2012; Verona, Javdani, & Sprague, 2011; Yoder, Longley, Whitbeck, & Hoyt, 2008). It relates very closely to the well-established distinction between internalizing and externalizing factors in children (Achenbach & Edelbrock, 1978). While many studies support hierarchical models, where the symptoms can load simultaneously on a single internalizing factor as well as on one or more symptom-specific factors (Mineka et al., 1998), other studies argue that the more parsimonious, *single higher-order factor model* that does not contain disorder-specific influences is sufficient in capturing the variance in depression and anxiety (Krueger & Finger, 2001). Independent of the model used, the internalizing factor has been found to be associated with different aspects of psychosocial and health dysfunction over and above symptom-specific impairment (Eaton et al., 2013; McGlinchey & Zimmerman, 2007; Simms et al., 2012). Many studies have found that neuroticism is at the core of the internalizing factor (Griffith et al., 2010; Hettema, Neale, Myers, Prescott, & Kendler, 2006). Overall, research exploring the internalizing factor indicates that individual disorders share a core psychopathological dimension, reflecting their shared clinical presentation, aetiology, likelihood of co-occurrence and treatment response. Furthermore, a recent study found that a single higher order factor may underlie all of psychopathology, not just internalizing disorders, suggesting that many of these characteristics are shared not only among different depression and anxiety disorders, but also with other disorders such as ADHD or eating disorders (Caspi et al., 2014).

Figure 1.2 - The hierarchical model of depression and anxiety



Note. V_s – variable-specific variance.

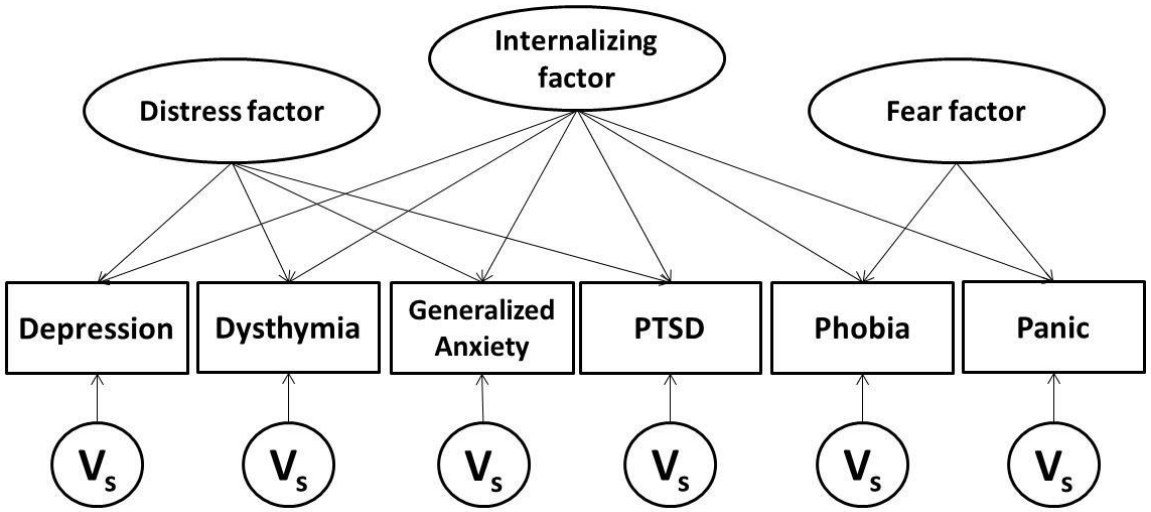
The model adapted from the hierarchical model of depression and anxiety proposed by Mineka et al. (1998).

Higher order sub-factors

The overarching internalizing factor does not reflect the observation that some disorders might be more closely associated with each other than others. This structure can be captured in the hierarchical models that allow individual disorders to load on the lower order sub-factors in addition to loading on the single internalizing factor. The lower order components of the internalizing spectrum are currently debated. One influential model organised different depression and anxiety symptoms into three sub-factor groups based on observed patterns of disorder co-occurrence: *distress*, *fear* and *bipolar* disorders (Watson, 2005) (Figure 1.3). The first two sub-factors are relevant to the current thesis. The *distress factor* explained covariation between depression, dysthymia, generalized anxiety and PTSD, over and beyond

the internalizing factor. Similarly, the *fear factor* explained the unique covariance between panic disorder and phobias. The distinction between distress and fear disorders has been confirmed in other studies in adults (Eaton et al., 2013; Keyes et al., 2013; Kotov, Perlman, Gámez, & Watson, 2014; Krueger, 1999; Kushner et al., 2013; Sellbom, Ben-Porath, & Bagby, 2008; Slade & Watson, 2006; Vollebergh et al., 2001; Watson, 2005), as well as in children (Lahey et al., 2004; Lahey et al., 2008; Prenoveau et al., 2010). The distress factor reflects the epidemiological evidence that generalised anxiety is more closely associated with depression than with other anxiety disorders, and adds to the much debated issue of diagnostic classification of generalized anxiety (Hettema, 2008a; Mennin et al., 2008; Moffitt et al., 2007).

Figure 1.3 - Distress and fear model of depression and anxiety



Note. V_s – variable-specific variance.

The model adapted from the model of depression and anxiety proposed by (Watson, 2005).

Stability of higher order structures

Studies of internalizing disorders structure are largely cross-sectional. To date only a handful of studies have investigated the stability of the higher order structure of depression and anxiety over time, together spanning periods between 2 months to 9 years (Eaton et al., 2013; Fergusson et al., 2006; Kotov et al., 2014; Krueger, Caspi, et al., 1998; Kushner et al., 2013; Vollebergh et al., 2001). These studies have found that the higher order factors are very stable across time, while the disorder-specific variation shows more mixed stability and might depend on the particular symptom type. In addition, a relatively small number of studies have investigated these theoretical models from a developmental perspective. Studies in young people generally encompass very wide age ranges spanning both childhood and adolescence, so it is unclear whether the higher-order structures change across development. To date one study of adolescents found that the higher order structure remained stable over a one-year period (Prenoveau et al., 2010). Another study found that the higher order structure replicated across both childhood and in adulthood, however the data on childhood psychopathology was collected retrospectively (Olino et al., 2008). Taken together, these studies tentatively suggest that the theoretical models of the higher order structure of depression and anxiety might be stable and applicable to multiple ages.

Considerations

It is important to highlight the limitations associated with basing theoretical models on the empirically and statistically derived structural relations between depression and anxiety. First, many studies used diagnostic measures of depression and anxiety, which carries several limitations (Watson, 2009). Specifically, the use of diagnoses might result in a loss of information due to the application of the categorical thresholds. The model fitting results might also be influenced by low prevalence rates of the psychiatric disorders, changing diagnostic criteria, diagnostic inconsistencies across studies and diagnostic unreliability. As different symptoms that comprise a disorder are embedded in the diagnostic categories, it is

impossible to estimate each symptom's individual contribution to the shared and disorder-specific factors. In addition, each symptom might be included in more than one diagnostic category, and for this reason it is unclear whether it is the overlapping definition boundaries that result in statistically derived higher order factors. Although studies conducted using the dimensional measures of depression and anxiety symptoms ameliorate many of the problems associated with diagnoses, they fail to provide information about how the derived structures relate to the DSM diagnoses, thus might have a limited clinical utility. Hybrid models that combine both the continuous and categorical components into the latent structure might address some of these limitations (Gros, McCabe, & Antony, 2013; Kotov et al., 2014). Notwithstanding these limitations, and although no single higher order model has achieved a universal acceptance, both the diagnostic and the symptom-level data strongly suggest that different depression and anxiety disorders share a substantial amount of their variance, with a potential subdivision into the distress and fear groups currently being debated. Finally, it is important to note that the higher order approaches to classifying internalizing disorders should not be seen as reductionist, as they do not dismiss the validity of different diagnoses, and the significant disorder-specific variance indicates that unique features of some disorders remain meaningful for differential treatment.

1.4.4. AETIOLOGY

Mechanisms of intergenerational transmission

Family and twin studies can provide insight into the shared aetiology of co-occurring disorders. Family studies can be used to test whether there is a disorder-specific intergenerational transmission of risk of a particular disorder or whether there is a common predisposition for two (or more) disorders. If there is an association between disorders, indicated by elevated

occurrence in parents and children, these disorders may be causally associated, or share common aetiology (shared familial influences). Alternatively, if there is no association between disorders, with disorder occurrence in parents not related to the occurrence in children, these disorders may not have shared aetiology. Research has assessed the intergenerational transmission of both depression and anxiety simultaneously, and the evidence from family studies generally suggesting common familial influences on depression and anxiety, as discussed below.

Although informative and representative of general singleton population, family studies nonetheless are limited as they are unable to disentangle genetic influences from shared environmental influences, such as parenting. Parental psychopathology may index both genetic and environmental risk, and thus family studies cannot provide information about the specific path of intergenerational transmission. Genetically sensitive designs such as twin and adoption studies are able to provide information about the relative contribution of genetic and environmental factors to transmission of comorbid psychopathology. Adoption studies allow to estimate the route of psychopathology transmission by comparing offspring characteristics to biological parents, who provide only genetic influences, and to adoptive parents, who provide only shared environmental influences. However, a major limitation of adoption studies is that they are not representative of general population, and genetic influence from biological parents cannot be disentangled from prenatal environmental influences, which may be particularly important in the aetiology of mental health. Another limitation of adoption studies is that adoptions are generally not random, with adoptive parents often matching the biological family on many characteristics. To overcome these limitations, twin studies are more commonly used to study intergenerational transmission of comorbid psychopathology, as they are able to disentangle disorder-specific and transdiagnostic genetic, shared and non-shared environmental influences. For this reason the current thesis focuses largely on finings obtained from twin studies, and uses quantitative genetics methodology to further understand these processes.

Common aetiological influences on depression and anxiety in family studies

Family studies indicate that depression and anxiety disorders moderately aggregate in families, suggesting that familial influences contribute to the co-occurrence of depression and different anxiety disorders, such as generalized anxiety (Kendler, Davis, & Kessler, 1997; Leckman, Merikangas, Pauls, Prusoff, & Weissman, 1983; Reich, 1995; Skre, Onstad, Edvardsen, Torgersen, & Kringlen, 1994), panic (Goes et al., 2012; Maier, Minges, & Lichtermann, 1995; Mendlewicz, Papadimitriou, & Wilmotte, 1993; Weissman, Leckman, Merikangas, Gammon, & Prusoff, 1984), and PTSD (Davidson, Tupler, Wilson, & Connor, 1998; Hudson et al., 2003). For example Kendler et al. (1997) investigated the intergenerational transmission of both internalizing (depression and generalized anxiety) and externalizing (alcohol and drug abuse, and antisocial personality) symptoms and found specificity in the transmission of the internalizing versus externalizing domain, but not in the transmission of specific symptoms within each domain. Furthermore, a recent study investigated intergenerational transmission of depression and a range of anxiety disorders (panic, generalized anxiety, PTSD, social and specific phobias) and found that the transmission is largely non-specific (Starr, Conway, Hammen, & Brennan, 2013). These studies suggest that individuals inherit a broad genetic and shared environmental risk for internalizing problems are fairly broad. However, other family studies found only disorder-specific, independent transmission of depression and anxiety within families, supporting presence of at least some disorder-specific factors (Klein, Lewinsohn, Rohde, Seeley, & Shankman, 2003; Mannuzza, Chapman, Klein, & Fyer, 1994; Weissman et al., 1993; Wickramaratne & Weissman, 1993). In sum, family studies that assessed specificity of intergenerational transmission of depression and anxiety disorders provide a mixed evidence for shared familial risk.

Common aetiological influences on depression and anxiety in twin studies

Twin studies in adults are much more consistent and generally find a high genetic overlap between depression and different anxiety disorders and symptoms, as well as a moderate non-

shared environmental overlap between them (Hettema, 2008b; Kendler, 1996; Kendler, Aggen, et al., 2011; Kendler, Gardner, Gatz, & Pedersen, 2007; Kendler, Neale, Kessler, Heath, & Eaves, 1992b, 1993a; Kendler, Prescott, Myers, & Neale, 2003; Kendler et al., 1995; Mosing et al., 2009; Roy, Neale, Pedersen, Mathe, & Kendler, 1995). Looking specifically at different anxiety types, depression and generalized anxiety share an almost complete genetic overlap (Kendler, 1996; Kendler et al., 2007; Kendler et al., 1992b; Roy et al., 1995). There is also a high genetic overlap between depression and panic (Kendler, Prescott, et al., 2003) and PTSD (Koenen et al., 2003), and a moderate genetic correlation between depression and specific phobias (Hettema et al., 2005; Kendler et al., 1993a). The pattern of the moderate-high genetic and the moderate non-shared environmental overlap is generally replicated in younger participants, when looking at the overlap between the depression/distress and total anxiety scores (Eley et al., 2003; Eley & Stevenson, 1999; Lahey, Van Hulle, Singh, Waldman, & Rathouz, 2011; Thapar & McGuffin, 1997; Zavos, Rijsdijk, et al., 2012), as well as the specific anxiety types such as social phobia (Nelson et al., 2000). However, to date very little work has been done looking at the shared aetiological influences between depression and different anxiety symptoms in young people (examined in Chapter 3). In addition, unlike in adults, shared environmental influences may also contribute to the overlap between depression and anxiety in young people (Eley et al., 2003).

Higher order aetiological structure

Only a handful of twin studies have investigated the higher order structure of internalizing psychopathology to test whether shared genetic influences underpin a single internalizing factor. Analyses in adults provide support for a single internalizing genetic factor influencing depression and anxiety (Goes et al., 2012; Kendler, Aggen, et al., 2011; Mosing et al., 2009). In addition, one study found separate genetic influences on distress (depression and generalized anxiety) and fear (animal and situational phobias) symptoms, with both genetic factors loading on panic symptoms (Kendler, Prescott, et al., 2003). Finally, studies in young people support a

single genetic factor influencing a range of internalizing symptoms (Cosgrove et al., 2011; Lahey et al., 2011; Silberg & Bulik, 2005; Silberg et al., 2001). However, studies in young people encompass broad age-ranges spanning childhood and adolescence, thus it remains unknown whether higher order structures are the same at specific developmental stages (examined in Chapter 3).

Aetiological influences on heterotypic continuity

Three longitudinal twin studies to date have investigated the genetic and environmental influences shared between depression and anxiety symptoms over time (Rice, van den Bree, & Thapar, 2004; Silberg & Bulik, 2005; Silberg et al., 2001). For example, one study found that the common genetic influences on childhood overanxious disorder and phobias continue to adolescence, where they also predict variance in adolescent depression (Silberg et al., 2001). In the same sample a single set of latent genetic influences loaded on depression, overanxious disorder, separation anxiety and eating disorder symptoms, measured first in childhood and then in adolescence (Silberg & Bulik, 2005). Finally, consistently with these findings another study has found, in a sample of young people aged 5-17 at baseline, that early anxiety symptoms and later depression symptoms were associated due to a shared genetic risk factor (Rice et al., 2004). These longitudinal twin studies suggest that genetic influences shared between depression and anxiety might contribute to the heterotypic continuity of these traits and maintain comorbidity over time. However, to date the degree to which stable and time-specific etiological influences are shared between depression and different anxiety disorder symptoms across development remains largely unknown (examined in Chapter 4).

Specific genetic and environmental influences

Taken together, the results from twin and family studies support the generalist genes hypothesis (Eley, 1997; Plomin & Kovas, 2005). Despite the high genetic overlap, to date no molecular study has identified specific genetic variants that contribute to the comorbidity

between depression and anxiety. In terms of the symptom-specific environmental influences, depression and anxiety might be associated with different negative life events. For example, one study found that childhood anxiety is uniquely associated with 'threat' events, such as experiencing trauma as a witness, while depression is uniquely associated with interpersonal problems and 'loss' events, such as a loss of an attachment figure (Eley & Stevenson, 2000). This pattern of results is supported in other developmental samples and in adults (Asselmann, Wittchen, Lieb, Höfler, & Beesdo-Baum, 2015; Finlay-Jones & Brown, 1981; Kendler, Hettema, Butera, Gardner, & Prescott, 2003; Williamson, Birmaher, Dahl, & Ryan, 2005). Furthermore, parenting behaviour can also differently influence depression and anxiety symptoms in children – one study found that parental rejection was more strongly associated with child depression, while parental control more associated with anxiety (Rapee, 1997). However, it is important to note that given the moderate non-shared environmental overlap between depression and anxiety, the role of the individual-specific environmental influences in depression-anxiety comorbidity should not be overlooked. Environmental influences can produce enduring and broad effects through biological and social changes in an individual (Kendler, Eaves, et al., 2011) and may include a range of risk factors that influence both depression and anxiety, such as some mixed threat-loss life events (Asselmann et al., 2015; Kendler, Hettema, et al., 2003), insecure attachment early in life (Lee & Hankin, 2009), and severe environmental stressors such as childhood maltreatment and natural disasters (Anda et al., 2006; Goenjian et al., 2005; Kendler et al., 2000). Future studies should continue to identify symptom-specific environmental influences, as well as those that contribute to the co-occurrence of depression and anxiety, to inform interventions and prevention strategies, as well as to identify at-risk individuals.

1.4.5. SUMMARY

Depression and anxiety co-occur across the lifespan, with comorbidity evident both cross-sectionally as well as across time. As comorbid depression and anxiety symptoms are associated with higher health burden than either condition alone, and may interfere with treatment, it is crucial to understand the association between these problems to inform transdiagnostic treatment. In the context of numerous limitations characterizing the current diagnostic manuals, multiple theoretical models have been proposed to explain why depression and anxiety co-occur. The existing literature does not universally support one higher order conceptualisation, but fundamentally each of the proposed theoretical models indicates that depression and anxiety disorders share a common as well as disorder-specific liability. Family and twin studies have been used to examine the aetiology of this shared liability and the results consistently suggest that depression and anxiety share a large proportion of their genetic influences, as well as a moderate proportion of non-shared environmental influences. The remaining non-shared environmental influences are disorder-specific, uniquely influencing each of the symptoms. Some of the latent genetic influences are also thought to operate in a stable manner and thus contribute to the co-occurrence of depression and anxiety across development.

1.5. BIASED COGNITION IN DEPRESSION AND ANXIETY

This section introduces cognitive biases that play a role in development and maintenance of depression and anxiety. First, a range of cognitive biases are outlined, focusing first on experimental measures of attentional and interpretational biases, followed by self-report measures of maladaptive cognitions. Second, one cognitive bias of particular interest to this

thesis, anxiety sensitivity, is described in closer detail. Third, transdiagnostic and specific processes and contents of cognitive biases to depression and anxiety are discussed. Finally, the relatively novel literature on aetiological influences on cognitive biases, as well as evidence for genetic and environmental influences common to cognitive biases and internalizing symptoms, is presented.

1.5.1. COGNITIVE BIASES

Biases in the way individuals attend to, interpret and remember emotional information (particularly negative information) have been implicated in the development and maintenance of internalizing symptoms and disorders in young people and adults (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van Ijzendoorn, 2007; Cisler & Koster, 2010; Field & Lester, 2010; Gotlib & Joormann, 2010; Hadwin & Field, 2010; Jacobs, Reinecke, Gollan, & Kane, 2008; Mathews & MacLeod, 2005; Muris & Field, 2008). Specifically, anxious and depressed individuals have consistently been shown to be sensitive to and biased towards negative information (such as the threat-related stimuli) in the environment at all stages of information processing. These biases are present both at the automatic information encoding stage (attentional biases), as well as at the later, interpretational stages (interpretation and memory biases). Such information processing biases increase the likelihood of perceiving danger in the environment, maintaining depression and anxiety symptoms as well as strengthening the existing maladaptive cognitions and vulnerabilities. Biased cognitions (e.g. recurrent thoughts of death and suicidal ideation) are also part of the diagnostic criteria for major depression episode (American Psychiatric Association, 2013). For this reason cognitive biases are targeted by the recommended first-line psychological interventions for internalizing problems such as CBT (AACAP, 2007a, 2007b). They are also central to potential novel treatment and prevention approaches such as attentional-bias modification (ABM) training

(Hakamata et al., 2010). Thus, understanding these processes in depth is of high clinical relevance.

Experimentally measured attentional biases

Cognitive biases have been measured using a range of different methods, which can broadly be divided into experimental paradigms and self-report questionnaires. Most commonly used cognitive experimental paradigms include reaction time measures such as the dot-probe (MacLeod, Mathews, & Tata, 1986) and emotional Stroop tasks (Williams, Mathews, & MacLeod, 1996), as well as tasks involving the interpretation of ambiguous, potentially threatening hypothetical situations (Barrett, Rapee, Dadds, & Ryan, 1996) or threat-neutral homophones (French & Richards, 1992). The first two methods have been commonly been used to study the attentional biases, and in essence these tasks compare reaction times to the neutral vs emotional stimuli, with faster reaction times towards the emotional information inferred as the attentional bias towards threat. For example, emotional Stroop task requires participants to identify the colour of stimuli varying in emotional valence whilst ignoring their emotional meaning. Slower reaction times for emotional stimuli compared to non-emotional stimuli indicates that processing the emotional meaning of the stimulus inhibited the simultaneous processing of colour, indicating an attentional bias. A recent meta-analysis of 29 empirical studies has found that depressed adults show attentional bias for negative stimuli, as compared to non-anxious controls (Peckham, McHugh, & Otto, 2010). Experimental studies in children have also indicated that the attentional biases are present in young people with depression symptoms (Joormann, Talbot, & Gotlib, 2007; Kyte, Goodyer, & Sahakian, 2005). Similarly, a meta-analysis of 172 studies has found that adults and children with anxiety disorders, as well as adults with anxiety symptoms, show attentional bias towards threatening information (Bar-Haim et al., 2007). Participants' baseline, as well as experimentally-induced negative attentional biases, were found to predict future depression and anxiety symptoms (Beevers & Carver, 2003; MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002;

Mathews & MacLeod, 2002), although the directionality of this relationship is debated (Van Bockstaele et al., 2014). In support of the causal role of cognitive biases in internalizing problems, recent efforts implementing the ABM interventions to reduce internalizing symptoms tend to be successful in adults (Beard, Sawyer, & Hofmann, 2012; Hakamata et al., 2010), although not in children (Cristea, Mogoașe, David, & Cuijpers, 2015). Taken together, the evidence supports the view that attentional cognitive biases plays a role in depression and anxiety. However, the effect sizes tend to be moderate and many studies in this field do not find significant differences on attentional bias between individuals with and without depression or anxiety (Dalgleish et al., 2003; Hadwin et al., 2003; Neshat-Doost, Moradi, Taghavi, Yule, & Dalgleish, 2000). This may be due to poor reliability of the experimental tasks such as dot probe, especially in child populations (Brown, Eley, et al., 2014; Eide, Kemp, Silberstein, Nathan, & Stough, 2002; Schmukle, 2005; Strauss, Allen, Jorgensen, & Cramer, 2005).

The visual search paradigm is a primary task used to investigate attentional priority when several stimuli compete for attention. In this paradigm participants are required to find and respond to a target stimulus that is embedded in a visual search array. In order to measure attentional bias, the threat value of the target and the distractors is manipulated, and attentional bias is generally indicated by faster reaction times to the threatening targets. The visual search task has been used less often than the dot probe, emotional Stroop or spatial cuing paradigms to measure the attentional biases. One advantage of the visual search paradigm that is relevant to the current thesis is that these tasks are often able to tease apart automatic and volitional attentional processes (see section 1.6.1). Visual search studies are relatively consistent in showing that anxious individuals have attentional biases towards negative and threatening information (Byrne & Eysenck, 1995; Gilboa-Schechtman, Foa, & Amir, 1999; Hadwin et al., 2003; Lipp & Waters, 2007; Öhman, Flykt, & Esteves, 2001; Rinck, Becker, Kellermann, & Roth, 2003; Rinck, Reinecke, Ellwart, Heuer, & Becker, 2005). For example, evolutionarily relevant stimuli such as spiders and snakes were found to capture

attention in all participants, but the effect was significantly stronger in individuals with phobia symptoms, and this attentional bias was specific to phobia-relevant information (Öhman et al., 2001). It is noteworthy that the existing visual search literature is strongly skewed towards investigating the attentional biases in anxiety rather than in depression, with one study suggesting that the hypervigilance to threat in visual search paradigms might be specific to anxiety (Hadwin et al., 2003). More visual search studies investigating attentional biases in depression alongside anxiety are needed (addressed in chapter 7).

Experimentally measured interpretational biases

Studies investigating interpretational biases using ambiguous stimuli tend to be more consistent than the attentional bias literature. When presented with ambiguous information, such as hypothetical vignettes of everyday situations, depressed adults and children are more likely to endorse negative interpretations than non-depressed individuals (Dearing & Gotlib, 2009; Mogg, Bradbury, & Bradley, 2006; Reid, Salmon, & Lovibond, 2006). Similarly, anxiety has also been found to be associated with negative and threatening interpretations of ambiguity (Barrett et al., 1996; Dineen & Hadwin, 2004; Dodd, Hudson, Morris, & Wise, 2012; Dodd, Stuijfzand, Morris, & Hudson, 2015; Hadwin, Frost, French, & Richards, 1997; Richards, Austin, & Alvarenga, 2001; Taghavi, Neshat-Doost, Moradi, Yule, & Dalgleish, 1999). A recent meta-analysis found that cognitive-bias modification methods that target negative interpretation biases are successful at reducing anxiety in adults, although the effect size was modest and the changes were not significant for depression (Hallion & Ruscio, 2011). Furthermore, studies training interpretation biases towards threat show an increase in anxiety symptoms in young people (Lester, Field, & Muris, 2011; Lothmann, Holmes, Chan, & Lau, 2011), suggesting a causal role of interpretational biases in anxiety. However, the role of the interpretational biases in pathogenesis of internalizing problems is still debated. For example, in a sample of preschool children, threatening interpretations of ambiguous information significantly predicted anxiety symptoms at 12 months follow up, but not at longer follow up

periods, indicating that the interpretational biases may only play a role in relatively short term maintenance of anxiety (Dodd et al., 2012). Other studies have found evidence for anxiety scores predicting threat interpretation biases (Creswell & O'Connor, 2011), indicating a reciprocal relationship between these processes. Finally, although the current thesis does not concern memory biases, there is some evidence in the literature that both anxious and depressed adults and children are more likely to remember negative than positive information (Cloitre, Cancienne, Heimberg, Holt, & Liebowitz, 1995; Coles & Heimberg, 2002; Dalgleish et al., 2003; Moradi, Taghavi, Neshat-Doost, Yule, & Dalgleish, 2000; Raes, Williams, & Hermans, 2009; Watts & Weems, 2006).

Self-reported cognitive biases

Cognitive biases in depression and anxiety can also be assessed with self-report questionnaires. These questionnaires contain items describing maladaptive or intrusive cognitions and thinking styles. One such thinking style closely related to internalizing symptoms is *rumination*, defined as the repetitive, negative reflections about the past events and experiences (Nolen-Hoeksema, 2000; Rood, Roelofs, Bögels, Nolen-Hoeksema, & Schouten, 2009). Another closely related maladaptive cognitive style that plays a role in internalizing symptoms is *pathological worry*, which reflects the concerns about the anticipated potential danger of future events (Chelminski & Zimmerman, 2003; McLaughlin, Mennin, & Farach, 2007; Starcevic et al., 2007). Furthermore, many studies have identified a range of other related cognitive biases and maladaptive thoughts processes that are closely associated with the internalizing problems. These include *hopelessness* – the generalized negative expectations of the future (Beck, Steer, Beck, & Newman, 1993; Beck, Wenzel, Riskind, Brown, & Steer, 2006; Brothers & Andersen, 2009; Miranda & Mennin, 2007), *negative attributional style* – an attribution of negative events to internal (directed to the self), stable (likely to persist over time) and global (likely to affect many aspects of life) causes, and positive events to external, unstable and specific causes (Ahrens & Haaga, 1993; Gladstone & Kaslow,

1995; Hankin, Abramson, & Siler, 2001) and *intolerance of uncertainty* – a tendency to react negatively to situations that are uncertain (Carleton, 2012; Carleton, Fetzner, Hackl, & McEvoy, 2013; Gentes & Ruscio, 2011; Holaway, Heimberg, & Coles, 2006; McEvoy & Mahoney, 2012). Thus, there is plenty of evidence suggesting that internalizing problems are characterised by a range of cognitive biases that can be assessed using self-report measures, but it is also important to note that these processes may be capturing overlapping constructs.

1.5.2. ANXIETY SENSITIVITY

Definition and higher order structure

One self-reported cognitive bias of interest for this thesis is anxiety sensitivity. Anxiety sensitivity is defined as an enhanced attention to the symptoms related to experiencing anxiety, such as the pounding heart or nausea, with a belief that they are harmful or have dangerous consequences (Reiss, Peterson, Gursky, & McNally, 1986; Taylor, 1999). As such, anxiety sensitivity constitutes both an attentional bias (hypervigilance to threat-relevant information) and an interpretational bias (endorsing negative belief about ambiguous information). For example, individuals with high anxiety sensitivity can be very vigilant to their increased heart rate when anxious, and believe that this is dangerous. This reaction further heightens their fears and may lead to a vicious cycle that maintains anxiety and could eventually culminate in a panic attack (Taylor & Fedoroff, 1999). Anxiety sensitivity can also lead to maladaptive coping strategies such as experiential avoidance, which is thought to amplify stress and increase risk of depression (Tull & Gratz, 2008; Zvolensky & Forsyth, 2002). It is important to highlight that anxiety sensitivity is distinct from trait anxiety. Trait anxiety refers to the extent to which an individual is fearful and prone to anxiety, while anxiety sensitivity is a fear of experiencing anxiety symptoms themselves (Taylor, 1996). A number of

studies have shown that anxiety sensitivity explains variance in anxiety over and above trait anxiety (Zinbarg, Brown, Barlow, & Rapee, 2001). Anxiety sensitivity is also not a unitary construct. Although there is a debate regarding the specific number and content of anxiety sensitivity subscales, confirmatory factor analytic studies (Wright et al., 2010) and a recent twin study (Brown et al., 2012) support a hierarchical structure of anxiety sensitivity, with three lower-order dimensions representing the physical, social and mental concerns. Specifically, the physical concerns subscale reflects the fear of bodily symptoms of anxiety (e.g. 'When my stomach hurts, I worry that I might be really sick'), the social subscale captures the fear of publicly observable symptoms of anxiety (e.g. 'I don't want other people to know when I'm afraid'), while the mental concerns subscale measures worries about cognitive control (e.g. 'When I am afraid, I worry I might be going crazy').

Cross-sectional associations with depression and anxiety

Anxiety sensitivity was originally proposed as a specific risk factor for panic disorder (Kearney, Albano, Eisen, Allan, & Barlow, 1997). In support of this, high anxiety sensitivity at age 7-14 years has been found to predict the first onset and maintenance of panic attacks concurrently during childhood (Calamari et al., 2001) as well as prospectively in adulthood (Maller & Reiss, 1992; Schmidt, Zvolensky, & Maner, 2006). Furthermore, CBT and pharmaceutical treatment of panic have been found to reduce anxiety sensitivity, with the decline in cognitive bias mediating the treatment effects (Simon et al., 2004; Smits, Powers, Cho, & Telch, 2004). Taken together, these studies provide evidence of shared developmental trajectory of anxiety sensitivity and panic disorder. However, other studies have shown relationship between anxiety sensitivity and a much broader range of anxiety subtypes, including PTSD and social phobia (Hazen, Walker, & Stein, 1994; Hensley & Varela, 2008; Naragon-Gainey, 2010; Olatunji & Wolitzky-Taylor, 2009; Schmidt et al., 2010; Taylor, 2003). Moreover, anxiety sensitivity is also associated with depression symptoms in young people and in adults (Naragon-Gainey,

2010; Olatunji & Wolitzky-Taylor, 2009; Weems, Hammond-Laurence, Silverman, & Ferguson, 1997).

Longitudinal associations with depression and anxiety

Finally, longitudinal studies have investigated whether anxiety sensitivity predates or is a consequence of depression and anxiety. Anxiety sensitivity predates a range of anxiety symptoms in childhood (Calamari et al., 2001; Waszczuk et al., 2013), suggesting that anxiety sensitivity might be a developmental cognitive risk factor for anxiety. Anxiety sensitivity also predicts future anxiety symptoms in older participants, over and above the baseline anxiety levels (Li & Zinbarg, 2007; Maller & Reiss, 1992; Schmidt et al., 2010; Schmidt et al., 2006; Weems, Hayward, Killen, & Taylor, 2002), although the evidence suggests that the relationship might be bidirectional. For example, Zavos, Rijsdijk, et al. (2012) found a reciprocal longitudinal associations between anxiety sensitivity and both depression and anxiety in adolescence, while another study found that the experience of panic and anxiety symptoms in adulthood lead to an increase in anxiety sensitivity (Schmidt, Lerew, & Joiner Jr, 2000). This suggests that anxiety sensitivity increases subsequent internalizing problems, but also that the internalizing symptoms can increase levels of anxiety sensitivity.

1.5.3. SPECIFICITY OF COGNITIVE BIASES

Cognitive-content specificity hypothesis

Information-processing biases have been found in both depressed and anxious individuals, yet these two populations have generally been studied separately with respect to cognitive vulnerabilities. However, there is a growing interest in transdiagnostic similarities as well as specificity of cognitive biases in depression and anxiety. From a theoretical point of view, the *cognitive content-specificity hypothesis* proposes that depression and anxiety share biased

cognitive *processes*, but can be differentiated by the *content* of emotional information that elicits the biases (Beck, Brown, Steer, Eidelson, & Riskind, 1987; Beck & Perkins, 2001; Clark & Beck, 1989). Specifically, the theory posits that while all internalizing disorders are characterised by maladaptive information-processing, depressed individuals tend to be biased towards negative information about the self and focus on experiences of loss, whereas the content of cognitive biases in the anxious individuals is thought to be predominantly focused on perceived threat or danger. In line with this model, the cognitive concerns targeted by CBT tend to vary across depression and anxiety disorders (Brewin, 1996). However, it is crucial to identify the shared as well as distinctive cognitive contents to inform both the transdiagnostic and the symptom-specific CBT treatment protocols.

Specificity of experimentally measured cognitive biases

Consistent with the cognitive content hypothesis, there is strong evidence that both depression and anxiety are characterised by biased experimentally-measured information *processing*, as discussed in section 1.5.1. However, there is some support in the cognitive experimental literature for different *content* of cognitive biases in depression and anxiety (Mathews & MacLeod, 2005). Some studies find that depression is uniquely associated with biases for loss stimuli, such as sad faces (Burkhouse, Siegle, & Gibb, 2014; Eizenman et al., 2003; Gibb, Benas, Grassia, & McGeary, 2009; Gotlib et al., 2004; Hankin, Gibb, Abela, & Flory, 2010), while anxiety is specifically characterized by biases towards threatening information, such as angry faces (Burkhouse et al., 2014; Dalgleish et al., 2003; Hadwin et al., 2003; Hankin et al., 2010; Mogg, Millar, & Bradley, 2000; Mogg, Wilson, Hayward, Cunning, & Bradley, 2012). For example, Hankin et al. (2010) have found that depressed-only children and adolescents showed attentional bias specifically to the sad facial expression, anxious-only youths were uniquely biased towards angry faces, while comorbid participants exhibited attentional biases to both types of facial expressions. However, many studies do not find this specificity for either one or both of the disorders (Dalgleish et al., 2003; Mogg & Bradley, 2005;

Salum et al., 2013). Finally, some studies have investigated the cognitive content specificity for distress vs fear disorders rather than for depression vs anxiety disorders (Salum et al., 2013; Waters, Bradley, & Mogg, 2014). For example one study used the dot probe paradigm and found that in children, the distress disorders predicted attentional bias towards threat, while the fear disorders predicted an opposite tendency of attentional bias away from threat (Salum et al., 2013).

Specificity of self-reported measures of cognitive biases

Maladaptive cognitive *processing* styles measured by self-report questionnaires are also generally found to have nonspecific associations with depression and anxiety. For example, *rumination* was originally investigated in the context of depression (Rood et al., 2009) and some studies support the view that rumination is specifically associated with depression (Brown, Meiser-Stedman, Woods, & Lester, 2014; Epkins, Gardner, & Scanlon, 2013; Hankin, 2008). However a majority of studies find that rumination is a transdiagnostic maladaptive cognitive process in both depression and anxiety (Broeren, Muris, Bouwmeester, van der Heijden, & Abee, 2011; McEvoy, Watson, Watkins, & Nathan, 2013; McLaughlin & Nolen-Hoeksema, 2011; Nolen-Hoeksema & Watkins, 2011; Olatunji, Naragon-Gainey, & Wolitzky-Taylor, 2013; Roelofs et al., 2009). Some studies looking at rumination subscales found specific associations of brooding (a passive and self-critical focus on one's mood symptoms) with depression, for example brooding has been found to significantly mediate the association between the negative affect and depressive symptoms, independently of anxiety (Verstraeten, Bijttebier, Vasey, & Raes, 2011). *Pathological worry* might be another transdiagnostic maladaptive cognitive processing style, as many studies point to its association with both depression and anxiety (Beck, Benedict, & Winkler, 2003; Broeren et al., 2011; Fresco, Frankel, Mennin, Turk, & Heimberg, 2002; McEvoy et al., 2013; Muris, Roelofs, Rassin, Franken, & Mayer, 2005; Young & Dietrich, 2015). On the other hand, there is evidence in the literature that *hopelessness* may be unique to depression (Beck et al., 2006; Beck et al., 2001; Miranda &

Mennin, 2007). Of note, while studies generally do not find that that maladaptive cognitive styles clearly differentiate between depression and anxiety, some identify stronger associations between certain maladaptive beliefs and specific internalizing problems (Hendriks et al., 2014; Verstraeten et al., 2011). For example, Hendriks et al. (2014) found that the levels of hopelessness, suicidality and rumination were significantly higher in depressed-only than in generalized anxiety-only patients, while the level of pathological worry was significantly higher in generalized anxiety-only than depressed-only patients, with comorbid cases showing more extreme cognitive profile, possibly reflecting higher severity of comorbid cases. Looking at the *content* of the maladaptive thoughts, a meta-analysis in which the cognitive content specificity hypothesis was evaluated has found no support for specificity of thoughts of harm and danger to anxiety, but confirmed that cognitions such as thoughts of loss and failure were unique to depressive symptomatology (Beck & Perkins, 2001).

Specificity of anxiety sensitivity

Anxiety sensitivity is of particular interest when considering the common and specific cognitive content in depression and anxiety. This is because anxiety sensitivity can be conceptualised both as a higher order maladaptive cognitive *process*, but also, given the three subscales (physical, social and mental concerns), provides information about the differential *content* of anxiety sensitivity. Two recent meta-analyses in adults found that anxiety sensitivity is associated with depression and a range of anxiety types (Naragon-Gainey, 2010; Olatunji & Wolitzky-Taylor, 2009). The associations were strongest between anxiety sensitivity and panic, general anxiety and post-traumatic stress disorder, suggesting a degree of specificity to certain anxiety disorders. In one meta-analysis total anxiety sensitivity was more closely associated with distress than fear disorders, but carries an incremental validity beyond these higher order constructs (Naragon-Gainey, 2010). Another meta-analysis of anxiety sensitivity in childhood and adolescence found a similar transdiagnostic pattern of results (Noël & Francis, 2011).

Overall, this strongly suggests that anxiety sensitivity is a transdiagnostic cognitive process (Boswell et al., 2013).

Looking at the specific dimensions of anxiety sensitivity, evidence suggests that the fear of physical sensations might be uniquely associated with anxiety in adults (Hendriks et al., 2014; Taylor, Koch, Woody, & McLean, 1996) as well as in young people (Brown, Meiser-Stedman, et al., 2014; Dehon, Weems, Stickle, Costa, & Berman, 2005; Joiner et al., 2002; Muris, 2002). However, some studies do not find this specificity (Grant, Beck, & Davila, 2007; McWilliams, Becker, Margraf, Clara, & Vriends, 2007). Regarding the social concerns/fear of publicly observable symptoms, evidence is again mixed, with some studies showing specificity to anxiety (Brown, Meiser-Stedman, et al., 2014; Taylor et al., 1996), especially social phobia (Muris, 2002; Naragon-Gainey, 2010; Rodriguez, Bruce, Pagano, Spencer, & Keller, 2004), while others find that social concerns characterise both depression and anxiety (Dehon et al., 2005; Hendriks et al., 2014; McWilliams et al., 2007; Viana & Rabian, 2009). There is a similarly mixed literature for the mental concerns/fear of cognitive dyscontrol anxiety sensitivity subscale, with some studies finding that this scale is specific to depression (Rodriguez et al., 2004; Taylor et al., 1996), while others indicate that the mental concerns are present both in depression and anxiety (Brown, Meiser-Stedman, et al., 2014; Dehon et al., 2005; Hendriks et al., 2014; Noel, Lewis, Francis, & Mezo, 2013; Schmidt, Lerew, & Joiner, 1998; Viana & Rabian, 2009; Zinbarg et al., 2001). One study found that mental concerns were elevated in generalized anxiety disorder as compared to other anxiety types, suggesting that this aspect of anxiety sensitivity might be particularly relevant to the distress disorders (Rector, Szacun-Shimizu, & Leybman, 2007). Overall, the results are mixed, but taken together suggest that there may be some specificity of physical concerns to anxiety, with the other two anxiety sensitivity subscales showing more broad associations with both depression and anxiety. However, only some studies controlled for the high covariance between depression and anxiety symptoms. Furthermore, the studies in the developmental samples did not include multiple age groups,

and for this reason were unable to investigate whether the associations between internalizing symptoms and anxiety sensitivity subscales change with age (addressed in chapter 5).

1.5.4. AETIOLOGY OF COGNITIVE BIASES

Genetically informative studies can provide information about the relative contribution of genetic and environmental influences to cognitive biases, as well as about the aetiological influences common to cognitive biases and internalizing symptoms. This is important given different theories regarding the aetiology of cognitive biases. Some suggest that the information-processing biases are in part a result of negative environmental influences such as abuse, which in turn lead to and contribute to the maintenance of internalizing disorders (Pollak, 2003). Consistent with this account, children who experienced maltreatment are more likely to have attentional bias to threat (Pine et al., 2005; Pollak, Cicchetti, Hornung, & Reed, 2000). Other environmental influences on cognitive biases may include negative parenting practices (Alloy et al., 1999). However, other studies point to genetic influences on cognitive biases, suggesting that maladaptive cognitive processes in part represent a genetic vulnerability to internalizing problems (Beck, 2008). This is supported by twin studies, as well as by evidence of associations between genetic variants implicated in the aetiology of internalizing problems, such as the short allele of serotonin transporter gene (5-HTTLPR), and cognitive biases (Beevers et al., 2011; Beevers, Wells, Ellis, & McGeary, 2009; Fox, Ridgewell, & Ashwin, 2009; Pergamin-Hight, Bakermans-Kranenburg, van IJzendoorn, & Bar-Haim, 2012; Thomason et al., 2010). To date only a handful of studies have investigated the aetiology of cognitive biases and their genetic and environmental associations with internalizing problems. One of the reasons is substantial methodological constraint, as genetically informative studies (especially twin modelling) require much bigger sample sizes than are generally used in cognitive psychology research.

Aetiology of attentional biases

Focusing on attentional biases, recognition of facial expressions such as anger has been found to be heritable (Lau et al., 2012; Lau et al., 2009), but it remains debated whether there are any genetic influences on the performance in experimental tasks measuring attentional biases. Twin studies conducted to date do not find genetic influences on experimental measures of threat avoidance, with the majority of variance explained by the latent non-shared environmental influences instead (Brown et al., 2013; Lau et al., 2012). It is important to note that non-shared environmental influences contain measurement error, which might be particularly high in the experimentally measured constructs. It remains unclear whether using more reliable measures of attentional bias would find genetic influences. Using a family design, Gibb et al. (2009) have found that children of mothers with depression history showed a significant attentional avoidance of sad faces, as compared to children of healthy mothers, which indicates familial influences on attentional biases. This association was stronger in children carrying the SS or SL genotype of the 5-HTTLPR marker, and in this group of children maternal depression was more likely to predict child's depression symptoms over time. The results are in contrast to the twin modelling studies and suggest that there may be a genetic association between attentional biases and depression. They are also in line with findings that attentional biases and internalizing symptoms might both be underpinned by the short variant of the 5-HTTLPR gene, suggesting shared genetic vulnerability (Beevers et al., 2011; Beevers et al., 2009; Fox et al., 2009; Thomason et al., 2010). Note however that the effect sizes associated with any type variant tend to be very small.

Aetiology of interpretational biases and attributional style

Only a handful of twin studies to date have investigated the aetiology of biased interpretations and negative attributional style. The first twin study of 8 years old children found that interpretational biases of the ambiguous information, as measured by homophone-words and ambiguous scenarios task, are moderately heritable, with the remaining variance explained by

non-shared environmental influences (Eley, Gregory, et al., 2008). Furthermore, the study found that both genetic and environmental influences contributed to the overlap between interpretational biases and depression symptoms. The second study, conducted in the same sample, investigated the aetiology of self-reported interpersonal cognitions and found that positive peer/self-perceptions and negative peer/self-perceptions were heritable and reflected overlapping genetic risks with depressive symptoms (Lau, Belli, Gregory, & Eley, 2014). Conversely, they found that negative expectations of peer and negative expectations of mother generally were influenced only by the shared and non-shared environmental influences, and had common environmental influences with depressive symptoms. Third, Chen and Li (2014) found that dysfunctional attitudes, indexed by a self-report measure of pervasive negative attitudes towards self and outside world, were moderately heritable in adolescence, with the remaining variance explained by the non-shared environmental influences. Finally, focusing on attributional style, twin studies in adolescence have identified both moderate genetic and high non-shared environmental influences in adolescence (Lau & Eley, 2008a; Lau, Rijsdijk, & Eley, 2006; Zavos, Rijsdijk, Gregory, & Eley, 2010). These studies have also found genetic and environmental overlap between attributional style, depression and anxiety symptoms. Taken together, twin studies are generally consistent in identifying that both genetic and environmental influences play an important role in the aetiology of biased interpretation and negative attributional style, and their associations with internalizing problems.

Aetiology of rumination

Rumination has also been found to be moderately heritable in adults and adolescents (Chen & Li, 2013; Johnson, Whisman, Corley, Hewitt, & Friedman, 2014; Moore et al., 2013), with one study identifying moderate shared environmental influences (Chen & Li, 2013), and with similar levels of genetic influences found for each subtype of rumination (Moore et al., 2013). These studies also found a high genetic and moderate environmental overlap between

rumination and depression symptoms. This is in line with the molecular studies investigating specific genetic influences on rumination, which have found that certain genetic variants such as the 5-HTTLPR short allele and the brain derived neurotrophic factor (BDNF) Val allele are associated with higher rumination levels (Hilt, Sander, Nolen-Hoeksema, & Simen, 2007; Stone, McGeary, Palmer, & Gibb, 2013). Studies looking at the genetic relationship between rumination and anxiety are currently lacking.

Aetiology of anxiety sensitivity

Relatively more research has been conducted into the aetiology of anxiety sensitivity. It is thought to arise due to the combination of the genetic predispositions and environmental influences, which are likely to begin in childhood (Zavos, Rijsdijk, et al., 2012). Numerous twin studies indicate that anxiety sensitivity remains moderately heritable across the lifespan, with the remaining variance accounted for by the non-shared environmental influences (Brown et al., 2012; Eley et al., 2007; Stein, Jang, & Livesley, 1999; Taylor et al., 2008; Zavos, Gregory, & Eley, 2012). Brown et al. (2012) found support for the hierarchical structure in adolescence, with common genetic and non-shared environmental influences acting via a higher-order factor in addition to subscale-specific influences. A twin study in adults also found genetic influences on the physical and mental concerns subscales, but only environmental influences on the social concerns subscale (Stein et al., 1999). In addition, another study found sex differences in the aetiology of anxiety sensitivity, with genetic influences evident only in females (Taylor et al., 2008). Both genetic and non-shared environmental influences are thought to contribute to the stability of anxiety sensitivity across adolescence, with new genetic influences emerging in late adolescence (Zavos, Gregory, et al., 2012). Very little is known about the genetic and environmental influences on the association between anxiety sensitivity and internalizing symptoms. To date, there are no multivariate twin studies investigating this relationship in adult twin samples. In adolescence, anxiety sensitivity and concurrent depression and anxiety symptoms were found to have high and significant genetic

correlations (Zavos et al., 2010). This suggests that genetic factors are important in the concurrent association between anxiety sensitivity and internalizing problems in adolescence. In childhood, high genetic correlations have been reported between anxiety sensitivity and panic, generalized and separation anxiety symptoms (Eley et al., 2007; Waszczuk et al., 2013). The results in childhood are consistent with the pattern found in the adolescent sample, and overall the literature suggests that anxiety sensitivity and internalizing problems co-occur due to both common genetic and non-shared environmental influences. However, the developmental age differences in these associations, as well as the specificity to depression have not been addressed. In sum, the extent to which genetic and environmental influences underpinning the relationship between anxiety sensitivity and the specific anxiety subtypes vary as a function of developmental stage remain largely unknown (addressed in chapters 5 and 6).

1.5.5. SUMMARY

Depression and anxiety are characterised by biased and maladaptive cognitions. Information processing biases include attentional biases, measured using a range of reaction time paradigms, interpretational biases, indexed by a range of tasks involving ambiguous information, and self-reported biases in cognitive styles such as anxiety sensitivity. Cognitive biases are thought to be a transdiagnostic process in depression and anxiety, for example attentional vigilance to threat and elevated levels of anxiety sensitivity have been found in both depression and anxiety. However different internalizing symptoms can be to some degree differentiated by the content of the biases. For example, there is converging evidence that thoughts of loss and failure are unique to depression, while anxiety sensitivity towards physical symptoms of anxiety are specifically associated with anxiety. However, more work needs to be done to systematically elucidate the disorder-specific vs transdiagnostic contents of the

cognitive biases. Finally, cognitive biases are thought to arise due to a combination of genetic and environmental influences, with twin studies identifying moderate heritability for most cognitive biases. The association between cognitive biases and internalizing symptoms is largely underpinned by shared genetic liability. To date no studies have addressed developmental age differences in the aetiology of cognitive biases, as well as the specificity of aetiological associations between depression and anxiety subscales.

1.6. COGNITIVE DEFICITS IN DEPRESSION AND ANXIETY

This section focuses on cognitive deficits characterising depression and anxiety. First, executive functions are defined and theoretical models embedded in the framework of cognitive control are presented. Second, the evidence for executive functioning deficits in depression and anxiety is outlined, with a focus on direction of effects and specificity to anxiety or depression. Third, mindfulness is defined within the cognitive control framework, and its associations with internalizing symptoms are discussed. The aetiology of mindfulness is then considered. Fourth, associations between cognitive biases and cognitive deficits are discussed, once again focusing on the evidence for directionality of effects. Finally, the relationship between mindfulness and cognitive biases, in particular anxiety sensitivity, is discussed, followed up by treatment implications.

1.6.1. EXECUTIVE FUNCTIONS

Definitions and components of executive functions

Cognitive functioning has been widely studied in internalizing problems, and impaired ability to think and concentrate is currently one of the criteria for the major depression and generalized anxiety disorder diagnoses (American Psychiatric Association, 2013). There is growing evidence for a broad cognitive impairment in depression and anxiety, irrespective of the threat relevance or emotional value of the information (Beaudreau & O'Hara, 2008; Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008; Eysenck & Derakshan, 2011; Hammar & Årdal, 2009; Joormann & Gotlib, 2010; Snyder, 2013). Specifically, it has been proposed that internalizing disorders and symptoms are characterised by executive function deficits. Executive function has been defined and labelled in many different ways in the psychological literature (e.g. cognitive control, central executive component of working memory), but at its core it is a higher order, top-down and effortful cognitive process, responsible for initiating, regulating and maintaining goal-driven behaviour and thoughts, such as inhibiting distracting information and switching between the task goals. Studies investigating the nature of executive functioning have found a unitary, higher-order executive functioning factor, as well as dissociable, lower-order factors (Baddeley, 1996; Miyake et al., 2000). According to one influential theory (Miyake et al., 2000), these specific factors reflect *updating* of information in working memory, measured on tasks such as the n-Back task (Harvey et al., 2005); the *shifting* between different tasks or rules, measured by paradigms such as the Wisconsin card sorting task (Buchsbaum, Greer, Chang, & Berman, 2005); and the *inhibition* of the dominant, automatic responses, measured by tasks such as the colour-word Stroop task (MacLeod, 1991). An overall executive function has been found to be very highly heritable, with specific genetic influences found for each of the executive function components, and independent from general intelligence or processing speed (Friedman et al.,

2008). Executive functioning is contrasted to automatic, bottom-up cognitive processes, such as routine repetition and dominant responses, for example reporting the written colour instead of the ink colour on incongruent trials of the colour-word Stroop task.

Theoretical models

Executive function is closely linked to attentional control, and embedded in this framework are the *dual-processing theories of attention*, which posit that attentional selection is determined by the competition of two attentional systems: a stimulus-driven, bottom-up attentional system, and a volitional, top-down attentional system (Corbetta & Shulman, 2002; Posner & Petersen, 1990). Attentional dysregulation is thought to underlie internalizing disorders, as it might be related to the ability to regulate emotions and responses to negative information (Cisler & Koster, 2010). One prominent theory based on the dual-processing conceptualisation is the *attentional control theory* (Derakshan & Eysenck, 2009; Eysenck, Derakshan, Santos, & Calvo, 2007). It proposes that trait anxiety impairs the efficiency of the executive function system, with bottom-up attentional selection mechanisms overpowering top-down attentional control system. As a result, anxious individuals are thought to have poorer shifting and inhibitory abilities, and to show more distractibility than non-anxious individuals, on a range of non-emotional cognitive tasks. Furthermore, attentional control theory proposes that in addition to executive functioning impairments indicated by poorer performance on psychological tasks, anxiety also results in lower processing efficiency, resulting in the increased activation of brain areas involved in a given task. Attentional control theory has been proposed specifically with relation to trait anxiety, and it is important to consider whether the same framework may apply to depression.

Inhibitory deficits in depression and anxiety

In support of attentional control theory, depressed and anxious individuals manifest deficits in several aspects of executive functioning. First, they show inhibitory deficits (Esterman et al.,

2013; Hammar et al., 2010; Hughes & Ensor, 2011; Moran & Moser, 2014; Moser, Becker, & Moran, 2012; Ursache & Raver, 2014), with a recent meta-analysis indicating that inhibition is the most impaired executive function in depression (Snyder, 2013). For example, Hammar et al. (2010) found that depressed adults had slower reaction times on incongruent trials of the colour-word Stroop task than healthy participants, indicating poorer inhibition of automatic responses. Another measure that directly assesses whether the bottom-up, automatic system is more dominant than the top-down, inhibitory system during the initial attention competition is the irrelevant singleton visual search task (Theeuwes, 1991, 1992). On this task participants perform a visual search for a target odd shape in an array of shapes, but on 50% of trials a salient, task-irrelevant color distractor is present. The slowing caused by the presence of a distractor indexes the amount of attentional capture via the bottom-up system, providing a direct measure of inhibitory attentional control (Theeuwes, 2010). The attentional capture as measured by this task was significantly correlated with trait anxiety (Moran & Moser, 2014; Moser et al., 2012) and symptoms of depression and PTSD (Esterman et al., 2013) in adults, supporting ACT. Finally, limited empirical evidence suggests that impaired inhibition, measured using either experimental tasks or self-report questionnaires of cognitive control, is associated with the internalizing symptoms in children and adolescents (Eisenberg et al., 2001; Hughes & Ensor, 2011; Mogg et al., 2015; Muris, Meesters, & Rompelberg, 2007; Ursache & Raver, 2014). This supports the attentional control theory in younger populations. However, the reliance on self-reported executive function in child research may be considered a limitation given that questionnaire measures of attentional control generally do not correlate highly with observed behavioral measures of the same construct (Muris, van der Pennen, Sigmond, & Mayer, 2008; Reinholdt-Dunne, Mogg, & Bradley, 2009). For this reason, inhibitory processes and attentional control theory warrant further exploration in child populations (addressed in chapter 7).

Shifting and updating deficits in depression and anxiety

Anxious and depressed individuals have also been found to have shifting and updating impairments on a range of tasks (Ansari, Derakshan, & Richards, 2008; Derakshan, Smyth, & Eysenck, 2009; Harvey et al., 2004; Lyche, Jonassen, Stiles, Ulleberg, & Landrø, 2010; Meiran, Diamond, Toder, & Nemets, 2011; Visu-Petra, Cheie, Benga, & Alloway, 2011). For example, Derakshan et al. (2009) have found that highly anxious adults were significantly slower in a task-switching paradigm than in a single task control condition as compared to low anxious controls. This is once again in line with attentional control theory. Finally, depression and anxiety are also characterised more broadly by dysfunction in episodic memory (Airaksinen, Larsson, & Forsell, 2005; Thomas et al., 2009) and impaired psychomotor skills (Ekornas, Lundervold, Tjus, & Heimann, 2010; Emck, Bosscher, Van Wieringen, Doreleijers, & Beek, 2011; Hill & Brown, 2013; Skirbekk, Hansen, Oerbeck, Wentzel-Larsen, & Kristensen, 2012). Furthermore, the evidence indicates that the severity of the cognitive impairment may be associated with the severity of the internalizing problems (Castaneda et al., 2008; Snyder, 2013), and some studies have found that the comorbid participants show the highest executive function deficits (Basso et al., 2007; Baune, McAfoose, Leach, Quirk, & Mitchell, 2009; Beaudreau & O'Hara, 2009; Beblo, Sinnamon, & Baune, 2011), which once again might index disorder severity. However, not all studies confirm this pattern (Castaneda et al., 2010; Lyche et al., 2010). Interestingly, cognitive dysfunction seems to persist even after the clinical recovery and may impair the daily life functioning after the disorder remission (Hammar & Årdal, 2009; Reppermund, Ising, Lucae, & Zihl, 2009; Rock, Roiser, Riedel, & Blackwell, 2014; Smith, Muir, & Blackwood, 2006; Snyder, 2013). Overall, the evidence suggests that cognitive impairments may constitute a core aspect of internalizing disorders, reflecting trait abnormalities of the neural circuits implicated in mood regulation.

Causality

The causal links between cognitive functioning and internalizing symptoms remain largely unknown, as very few studies have used longitudinal or developmental designs to study the direction of this association. First, executive functioning and internalizing problems could be due to shared risk factors, such as genes, neurobiological factors and stress exposure. Second, internalizing problems could lead to executive function deficits, either due to functional or structural brain changes associated with these conditions that also seem to play a role in cognition, such as lower hippocampal volume (Frodl et al., 2006; MacQueen & Frodl, 2011; McKinnon, Yucel, Nazarov, & MacQueen, 2009), or because the cognitive biases that characterize internalizing problems deplete cognitive resources. For example, experimentally induced rumination has been found to decrease depressed participants' inhibitory capacities, suggesting that maladaptive cognitive styles may interfere with executive functions (Philippot & Brutoux, 2008; Watkins & Brown, 2002). This is in line with attentional control theory, which proposes that trait anxiety impairs the efficiency of executive functions (Eysenck & Derakshan, 2011). However, findings that the cognitive impairment persists even after internalizing symptoms have remitted suggests that cognitive impairment is not purely a result of the presence of the disorder (Reppermund et al., 2009). Third, cognitive impairment could lead to the development and maintenance of internalizing problems, for example by maintaining cognitive biases and interfering with daily functioning and coping methods such as problem solving (Jaeger, Berns, Uzelac, & Davis-Conway, 2006). The relationship between cognitive biases and cognitive functioning is discussed in more detail in section 1.6.3.

Specificity

Relatively little is known about the specificity of cognitive deficits to depression and different anxiety types, as not many studies to date have directly compared executive functioning in different disorders. In general, studies looking at a range of depression and anxiety disorders and symptoms, as well as other disorders such as OCD, ADHD, schizophrenia and bipolar

disorder, find the association with impaired cognitive functioning, suggesting that it might be a transdiagnostic factor (Goschke, 2014; Snyder, Miyake, & Hankin, 2015). However, there is some initial evidence that an inhibition deficit might be uniquely associated with anxiety and not depression (Beaudreau & O'Hara, 2009; Lyche, Jonassen, Stiles, Ulleberg, & Landrø, 2011; Thomas et al., 2009). Looking at anxiety without social phobia vs social phobia, a recent study in children found that impaired inhibition was unique to the anxious group that did not have social phobia (Harvey et al., 2004; Mogg et al., 2015). Given the heterogeneity of both executive functions and internalizing problems, further work is needed to systematically elucidate the specificity of cognitive deficits to depression and anxiety (addressed in chapter 7).

1.6.2. MINDFULNESS

Definition and links to cognitive control

Mindfulness is defined as a non-judgemental awareness of the present moment experience (Bishop et al., 2004; Brown & Ryan, 2003). It is often conceptualised and measured as a trait, indexing individual differences in the dispositional tendency to be mindful in everyday life. Mindfulness has also been studied in the context of clinical interventions, such as the mindfulness-based cognitive therapy, which aims to improve mindfulness skills for therapeutic processes. In both conceptualisations, mindfulness involves top-down cognitive control (Chiesa, Serretti, & Jakobsen, 2013), first over the allocation, sustaining and shifting attention, which is necessary to remain focused on the present moment experience and to prevent mind wandering. Second, mindfulness involves cognitive control over the content of thought processes and interpretational style, which is required in order to achieve a non-judgemental and accepting attitude. Thus, mindfulness therapies have at their core aspects of attentional

training, akin to ABM, as well as cognitive restructuring, similar to CBT. In line with this conceptualisation, mindfulness is associated with a range of executive functions, such as performance measures of sustained attention and working memory (Chambers, Lo, & Allen, 2008; Mrazek, Franklin, Phillips, Baird, & Schooler, 2013; Valentine & Sweet, 1999). Two recent meta-analyses confirmed that mindfulness training increases performance on a range of objective measures of executive function (Chiesa, Calati, & Serretti, 2011; Eberth & Sedlmeier, 2012), indicating that these two constructs are closely related.

Mindfulness and internalizing symptoms

Mindfulness has a protective role in mental health (Keng, Smoski, & Robins, 2011) and group-based mindfulness behavioural cognitive therapy is currently recommended in the UK for adults at a significant risk of depression relapse (National Collaborating Centre for Mental Health, 2010). Several meta-analyses have confirmed that mindfulness interventions are successful at treating and reducing symptoms of depression and anxiety (Chen, Berger, et al., 2012; Chiesa & Serretti, 2010; Hofmann, Sawyer, Witt, & Oh, 2010; Piet & Hougaard, 2011). Mindfulness therapies have also been found to be useful in treating internalizing problems in childhood and adolescence (Burke, 2010). A recent study has found that mindfulness therapy is as successful as antidepressants in the prevention of depressive relapse in adults at risk for depressive relapse or recurrence (Kuyken et al., 2015). However, some of the limitations of the studies to date are noteworthy, for example many do not utilise control groups or compare the effectiveness of the mindfulness intervention to weak control interventions, such as reading. It would be informative for clinical practice to investigate whether mindfulness therapies are more effective or perform differently to other psychological approaches such as CBT. Some initial studies indicate that mindfulness based interventions may be less efficacious than the standard CBT (Manicavasgar, Parker, & Perich, 2011; Piet, Hougaard, Hecksher, & Rosenberg, 2010). Outside the clinical literature, *trait* mindfulness has significant negative association with both depression (Brown & Ryan, 2003; Cash & Whittingham, 2010) and

anxiety (Dekeyser, Raes, Leijssen, Leysen, & Dewulf, 2008), as well as more broadly with negative affect and neuroticism (Giluk, 2009), confirming the strong link between mindfulness and internalizing problems. Looking at the specificity of this relationship, Desrosiers, Klemanski, and Nolen-Hoeksema (2013) investigated the unique associations between different aspects of mindfulness, depression and anxiety. They found that the lack of non-judgemental attitude was significantly associated with depression, the poor capacity to label internal experiences with words was unique to anxiety, the poor nonreactivity (allowing thoughts and feelings to come and go without reacting or fixating on them) was associated with both depression and anxiety, while attending to the present moment was not associated with internalizing symptoms. Further work is needed to investigate disorder-specific and transdiagnostic aspects of mindfulness.

Aetiology of mindfulness

Relatively little is known about the aetiology of mindfulness. Individual differences in complex traits such as mindfulness are presumed to have arisen through an interaction of inherited predisposition and environmental circumstances, such as explicit training (Davidson, 2010). However, despite the clinical importance of mindfulness, the relative role of genes, shared environment and individual-specific experiences is unknown. Furthermore, focusing on the aetiology of the joint associations between mindfulness and internalizing problems may help to clarify some of the mechanisms that underpin this relationship. Recent studies point to epigenetic regulation of the inflammatory pathways as one of the mechanisms underpinning mindfulness-based interventions (Kaliman et al., 2014). Other biological pathways associated with mindfulness that may benefit mental health could include positive regulation of brain, endocrine and immune function (Creswell, Way, Eisenberger, & Lieberman, 2007; Ludwig & Kabat-Zinn, 2008). From a cognitive perspective, mindfulness might be associated with increased tolerance of negative thoughts, emotions and experiences, leading to a reduction of experiential avoidance. The attitude of acceptance might prevent negative interpretations,

while the focus on the present moment experience might make individuals' less likely to engage in negative repetitive thought processes such as rumination (van der Velden et al., 2015). The ways in which mindfulness might interact with cognitive biases is discussed in more detail in section 1.6.3. Genetically-informative studies can provide insight into the relative contribution of genetic and environmental influences to the relationship between mindfulness and internalizing problems. It is plausible that these traits show high genetic overlap, in line with the generalist genes hypothesis. However, mindfulness is associated with a range of other traits, for example, self-esteem, physical well-being, and personality traits such as conscientiousness, agreeableness, and openness to experience (Brown & Ryan, 2003; Giluk, 2009). Thus, genetic influences on mindfulness may be largely distinct from those influencing internalizing problems. Instead, environmental influences such as parenting or life events, may explain the relationship between mindfulness and internalizing symptoms. Investigating the role of genes and environment in the relationship between mindfulness and internalizing problems will help to understand the relative role of the biological and social mechanisms that link these traits (addressed in chapter 6).

1.6.3. Relationship between cognitive deficits and biases

Although internalizing disorders are characterised by both executive function deficits and cognitive biases, to date these cognitive processes have largely been studied separately. It is becoming increasingly clear that cognitive deficits and biases are closely related, and their relationship may play a crucial role in the development and maintenance of internalizing problems (Banich et al., 2009; Crocker et al., 2013). The main finding in the literature to date is that cognitive biases are more likely to be observed in the depressed and anxious individuals who have poor cognitive control. For example, Derryberry and Reed (2002) found that only anxious adults who self-reported low cognitive control showed difficulty disengaging attention

from threat, while anxious adults with good cognitive control did not show this attentional bias. Other studies replicated a similar pattern of results, in adults (Gorlin & Teachman, 2014; Peers & Lawrence, 2009; Reinholdt-Dunne et al., 2009; Richey, Keough, & Schmidt, 2012), as well as in young people (Lonigan & Vasey, 2009; Salemink & Wiers, 2012; Susa, Pitică, Benga, & Miclea, 2012; Verstraeten, Vasey, Raes, & Bijttebier, 2009). For example, Lonigan and Vasey (2009) found that self-reported effortful control moderated the association between negative affectivity and attentional threat bias in the dot probe task in a child sample.

Directionality of associations – cognitive biases cause cognitive control deficits

Cognitive deficits and biases are associated with each other. For example, in one study individuals who ruminate showed impairment on the Wisconsin Card Sorting Task, even when they were given feedback that the rule they were following was no longer correct (Davis & Nolen-Hoeksema, 2000). However, the directionality of this association remains unknown. It has been argued that cognitive biases impair executive functions. This might be because cognitive biases such as recurrent negative thoughts can deplete individual's processing capacity, and this additional cognitive load is thought to impair executive functions (Philippot & Brutoux, 2008; Watkins & Brown, 2002; Whitmer & Gotlib, 2012). For example, Philippot and Brutoux (2008) experimentally induced rumination and found that it impaired performance on the colour-word Stroop task in young adults. Furthermore, Connolly et al. (2014) found that rumination prospectively predicted impaired executive function in adolescence, while controlling for baseline executive function, whilst the reverse effect was not true.

Directionality of associations – cognitive control deficits cause cognitive biases

However, the opposite direction of causality is plausible. Emotional stimuli are salient (McNally, 1995; Pessoa & Ungerleider, 2004) and there are different mechanisms through which impaired executive function could lead to cognitive biases. First, emotional information

can capture the bottom-up, automatic attentional processes, such as when the threatening information is present in the visual field. Poor inhibitory abilities could impair the attention allocation, resulting in difficulties inhibiting threatening information on emotional tasks as well as in everyday life, which in turn can give rise to the attentional bias towards threat. Second, emotional information may be preferred by automated repetitive thought processes, such as negative interpretational biases, rumination or pathological worry. Impaired inhibition and shifting could lead to the inability to stop these intrusive and maladaptive recurrent thoughts. This is in line with the *impaired disengagement hypothesis* (Koster, De Lissnyder, Derakshan, & De Raedt, 2011), which posits that ruminators are characterised by an impaired attentional disengagement from the negative self-referent information. In support of the view that impaired attentional control leads to increased rumination, De Lissnyder et al. (2012) found that participants' shifting ability predicted rumination levels in response to stress six weeks later. Furthermore, Bredemeier and Berenbaum (2013) found that performance on an updating task predicted levels of worry several weeks later, even when controlling for baseline worry levels. Third, sub-optimal executive function could make it more difficult for individuals to initiate and maintain coping behaviours, problem solving and reappraisal, which involves reinterpreting the emotion invoking stimulus as non-emotional (Gross, 1998). Taken together, it is plausible that executive function deficits may lead to impaired emotion regulation, thus contributing to cognitive biases. Overall, the evidence suggests that dominant top-down cognitive control might be necessary to regulate processing of emotional information. However, the causal links between different cognitive deficits and biases, as well as the mechanisms underpinning this pathway, warrant further investigation, and it is plausible that bidirectional effects are in place. Two additional questions remain unanswered to date. First, as all of the studies used separate tasks to measure cognitive control and biases, it remains unknown whether and to what degree the biases might in fact reflect poor cognitive control rather than solely the selective processing of emotional (e.g. threat) stimuli. Second, to date

very little work looking at the association between executive control and cognitive biases has been conducted in children (addressed in chapter 7).

Mindfulness and cognitive biases

A separate line of evidence about the role of top-down cognitive control in the modification of cognitive biases comes from research on the association between mindfulness and maladaptive thinking styles. Mindfulness requires engagement of top-down cognitive processes and mindfulness training improves a range of executive functions (Chiesa et al., 2011; Eberth & Sedlmeier, 2012). There are number of mechanisms through which mindfulness could impact cognitive biases (Gu, Strauss, Bond, & Cavanagh, 2015; van der Velden et al., 2015). First, the non-judgemental and compassionate attitude might prevent dysfunctional and threatening interpretations and negative attributional style, as well as increase tolerance of negative thoughts. In support of this view, self-compassion was found to mediate the association between mindfulness training and both depression and anxiety (Bergen-Cico & Cheon, 2014; Kuyken et al., 2010). Second, mindful individuals might be better able to recognise the automatic negative cognitive processes such as rumination and pathological worry, and disengage from these thoughts by redirecting attention to the present moment experience. In line with this view, trait mindfulness is associated with lower levels of uncontrollable rumination (Jain et al., 2007; Raes & Williams, 2010) and worry (Sugiura, 2004). Mindfulness training has been found to reduce rumination (Van Vugt, Hitchcock, Shahar, & Britton, 2012) and worry (Delgado et al., 2010), and the evidence suggests that the decrease in rumination and worry mediates the association between the mindfulness training and the decrease of internalizing symptoms (Batink, Peeters, Geschwind, van Os, & Wichers, 2013; Desrosiers, Vine, Klemanski, & Nolen-Hoeksema, 2013; Gu et al., 2015; Shahar, Britton, Sbarra, Figueredo, & Bootzin, 2010; Van Aalderen et al., 2012; van der Velden et al., 2015). Furthermore, one study found that rumination uniquely mediates the association between mindfulness and depression, while worry uniquely mediates the association between

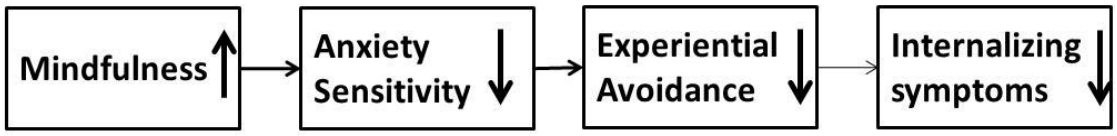
mindfulness and anxiety (Desrosiers, Vine, et al., 2013). Third, mindfulness training can reduce attentional biases for negative information (De Raedt et al., 2012). One study demonstrated an association between an improved sustained attention due to mindfulness training and a reduction in depression (Chambers et al., 2008). Taken together, these studies suggest that the top-down cognitive processes characterizing mindfulness reduce a range of cognitive biases, and that this reduction in cognitive biases might explain some of the association between mindfulness and internalizing symptoms.

Mindfulness and anxiety sensitivity

Another cognitive mechanism through which mindfulness may improve internalizing problems is by reducing anxiety sensitivity. The fear of anxiety-related sensations that characterises anxiety sensitivity is thought to contribute to experiential avoidance, which in turn amplifies the impact of emotional distress and may maintain depression and anxiety symptoms. Experiential avoidance has been found to mediate the association between anxiety sensitivity (specifically social and mental subscales) and depressive symptom severity (Tull & Gratz, 2008; Zvolensky & Forsyth, 2002). Mindfulness is thought to provide cognitive control that allows patients to increase their interoceptive exposure and bodily awareness in a self-compassionate manner. This is thought to allow patients to gain a more objective perception of the level of personal threat, rather than responding in a catastrophizing way. When attending to the experiences in a non-judgmental and open manner, the individual may become desensitized to the distressing sensations, thoughts and emotions that otherwise would be avoided. In support of this model, mindfulness training improved somatic and autonomic regulation (Delgado et al., 2010) and decreased anxiety sensitivity (Tanay, Lotan, & Bernstein, 2012). McCracken and Keogh (2009) found that in chronic pain patients, mindfulness reduces the impact of anxiety sensitivity (again the social and mental concerns) on emotional distress. Furthermore, Vujanovic, Zvolensky, Bernstein, Feldner, and McLeish (2007) found a significant interaction between anxiety sensitivity and mindfulness in predicting anxious arousal

symptoms and agoraphobic cognitions. Specifically, individuals with both low mindfulness and high anxiety sensitivity showed the highest levels of anxiety. Taken together, the evidence suggests that mindfulness reduces anxiety sensitivity, which in turn leads to a decrease in internalizing symptoms (Figure 1.4). However, this relationship has not been studied in young people. Furthermore, the aetiology of the association between mindfulness and anxiety sensitivity in any age group has not yet been investigated (both issues addressed in chapter 6).

Figure 1.4 - Mindfulness, anxiety sensitivity and internalizing problems



Implications for treatment

Understanding the link between executive functions and cognitive biases in depression and anxiety is important to inform clinical practice. First, persisting executive functioning deficits may interfere with coping mechanisms and psychological treatments. For example they could lead to lower the efficacy of CBT, as psychological therapy is cognitively demanding (Mohlman & Gorman, 2005). Second, given that the cognitive deficits continue after disorder remission, they might contribute to a reduction in life functioning and thus increase the risk of relapse (Hammar & Årdal, 2009; Jaeger et al., 2006). Third, the evidence discussed in this section suggests that executive functioning deficits play an important role in the maintenance of cognitive biases, and points to cognitive deficits as a more useful intervention target than cognitive biases (Koster et al., 2011). Future research should explore whether established therapies such as CBT, as well as novel approaches such ABM, improve overall attentional control. As cognitive control seems to be impaired in both depression and anxiety, it might

provide a transdiagnostic treatment target that may also transfer to other important areas such as daily functioning. Mindfulness based therapies provide one successful approach based on cognitive training to reduce internalizing symptoms. However, other forms of cognitive training that target specific cognitive domains might be a potential treatment and prevention focus for internalizing problems (Siegle, Ghinassi, & Thase, 2007). Preliminary evidence suggests that cognitive control training might be successful at reducing cognitive biases (Hoorelbeke, Koster, Vanderhasselt, Callewaert, & Demeyer, 2015) and internalizing symptoms (Callinan, Johnson, & Wells, 2014; Roughan & Hadwin, 2011). However, the effectiveness of such cognitive training approaches is currently debated (Shipstead, Hicks, & Engle, 2012; Wass, Scerif, & Johnson, 2012). Importantly for targeting childhood mental health problems, younger participants seem to benefit more from cognitive training than adults (Wass et al., 2012), possibly reflecting greater neural and behavioral plasticity earlier in development. Overall, investigating how to target both cognitive functions and biases might provide an important avenue for improvement of current treatment methods, as well as development of new therapeutic approaches.

1.6.4. SUMMARY

Both depression and anxiety are characterised by a range of cognitive function deficits, such as impaired attentional control and low mindfulness. Although the directionality of this effect is not fully established and bidirectional relationships are likely, the cognitive deficits are thought to contribute to the aetiology and maintenance of internalizing symptoms. Treatment approaches that target these deficits, such as mindfulness training, have been found to be very successful in reducing depression and anxiety. One of the mechanisms through which the cognitive impairment might influence depression and anxiety is by increasing cognitive biases. Understanding the link between cognitive abilities, maladaptive thought processes and

internalizing problems is informative for clinical practice, as cognitive deficits may interfere with treatment. Targeting these deficits might provide fruitful avenues for future transdiagnostic interventions.

1.7. AIMS AND STRUCTURE OF THE THESIS

The current thesis uses genetically informative, longitudinal and experimental designs to study (i) the genetic and environmental influences on depression, anxiety and their co-occurrence across development and (ii) three cognitive processes involved in child and adolescent depression and anxiety: anxiety sensitivity, mindfulness and attentional control. All empirical chapters represent papers that are either published or currently under review for publication. This thesis confers to King's College London guidelines for PhD theses incorporating publications.

Chapter 2 of this thesis provides an overview of the twin samples used in the analyses and discusses the twin methodology.

The following two empirical chapters (chapters 3 and 4) use twin modelling methodology to investigate the developmental associations between depression and four different anxiety disorder symptoms. **Chapter 3** examines the phenotypic and genetic structure of the symptoms cross-sectionally in childhood, adolescence and young adulthood. It provides evidence for developmental differences in the aetiology of the relationship between depression and anxiety, with the genetic influences becoming less disorder-specific from adolescence.

Chapter 4 focuses on the continuity and change of the genetic and environmental influences on depression, anxiety disorder symptoms and their co-occurrence across adolescence and

young adulthood. The study finds that both stable and newly emerging genes contribute to the comorbidity between depression and anxiety across this developmental period. Additionally, the results provide initial evidence that some non-shared environmental effects contribute to the stability and longitudinal co-occurrence of depression and anxiety disorder symptoms.

The remaining three empirical chapters (chapters 5-7) investigate the cognitive processes involved in the aetiology and maintenance of depression and anxiety. **Chapter 5** uses twin modelling methodology to investigate the associations between anxiety sensitivity dimensions and both depression and anxiety disorder symptoms cross-sectionally across development. The results identify disorder-specific versus shared cognitive content in depression and anxiety that are stable across development and underpinned by broad genetic vulnerability to the three traits.

Chapter 6 continues to investigate the association between depression and anxiety sensitivity, in the context of the first twin study of mindfulness. The analysis focuses on the attentional control aspect of trait mindfulness, given the established association between low attention control and internalising symptoms. The study suggests that adolescent trait mindfulness is moderately heritable, and provides preliminary evidence that the association between mindfulness, depression and anxiety sensitivity is largely due to shared genetic liability.

Chapter 7 revisits the question of disorder-specific versus shared cognitive processes in depression and anxiety. It is an experimental study investigating attentional control in middle childhood. The results suggest that both depression and anxiety symptoms are independently associated with poorer attentional control. This attentional deficit may account for some of the attentional biases often observed in anxious and depressed children on tasks investigating processing of emotional stimuli.

Chapter 8 provides a discussion of the empirical findings, their implications for research and practice, relevant limitations associated with this work and suggestions for possible future directions.

2. METHODS

2.1. OVERVIEW

This chapter provides an overview of the methodology used in the current thesis. First, the samples used are outlined. Next, the measures used to assess a range of constructs investigated in this thesis are described. Finally, the twin methodology is presented, including the twin design, different models fitted and some relevant assumptions and considerations.

2.2. SAMPLES

The current thesis uses three twin samples and one singleton sample that span childhood, adolescence and young adulthood, in order to examine both the phenotypic and aetiological associations between depression, anxiety and cognitive processes. An outline of the selection process and participant characteristics for each sample are presented in this section.

2.2.1. CHILD TWIN SAMPLE: ECHO

The Emotions, Cognitions, Heredity and Outcome (ECHO) twin study is a longitudinal sample of 300 twin pairs aged 8 years (mean age = 8 years 6 months, age range =8 years 2 months to 8 years 11 months) at wave 1 and about 10 years (mean age = 10 years 1 month, age range =9 years 7 months to 10 years 10 months) at wave 2. For both waves, parents/guardians provided written informed consent via the post prior to data collection. The study was granted ethical approval by the Maudsley Hospital Ethics Committee, London, United Kingdom (ref: 020/20).

The recruitment details and sample characteristics are described in Gregory, Rijsdijk, and Eley (2006). Chapters 3 and 5 of this thesis use both waves of the ECHO study.

The ECHO study is a spin-off from a larger longitudinal sample of twins born in England and Wales during 1994-1996 (TEDS, see section 2.2.3) (Trouton, Spinath, & Plomin, 2002). In order to maximise power and include children with high emotional symptoms, twins were recruited using a selected extremes design. The majority of twins were recruited due to one or both of them scoring within top 15% on child anxiety at age 7, as reported by parents. A smaller group of 'control' pairs were chosen, out of which none of the twins scored above the 15% threshold on anxiety symptoms. The following selection process was used. Out of 5,343 families in TEDS on whom parent-report anxiety data was available at 7 years, 1,378 had at least one child scoring within top 15% on child anxiety and the remaining 3,965 families were eligible for control group. Of these available families, 3,791 had to be excluded due to a number of exclusion criteria - withdrawn from TEDS (N = 30 pairs), child had a major medical condition (N = 177 pairs), participated in other concurrent studies (N = 948 pairs), lived outside two-hour travel radius from London (N = 2,606) and were untraceable (N = 30). This left 381 (28%) potential anxiety group families, of which 247 (65%) agreed to participate, and 1,171 (31%) potential control families, from which 92 were randomly invited to participate, of whom 53 (58%) agreed. This resulted in a total sample size at wave 1 of 300 twin pairs and this selection ensured that the data represented a full range of scores on test measures. Following testing, a further 11 twin pairs (4%) were excluded because at least one of the twins had a co-morbid diagnosis of a neurological impairment, autistic spectrum disorder, severe receptive language impairment or persistent attentional difficulties. Consequently, approximately 2 years later (mean = 1 year 7 months, SD = 3 months) 289 twin pairs were invited to participate in wave 2. Of these, 250 twin pairs (87% of wave 1 sample) were retested.

Of the families invited to participate in the ECHO study, those who agreed to take part were of a higher socio-economic status (SES), as measured by the parental qualifications and

employment, as well as mother's age at the birth of her first child, than the families who did not take part ($t(809)= 4.93$, $p<.01$). Furthermore, both female and male monozygotic pairs were more likely to take part than DZ pairs (14% vs. 10% opted in and out of the study, respectively, for MZ males and 19% vs. 15% for MZ females) and DZ male pairs were less likely to take part than DZ female pairs (10% vs. 15%, respectively, $\chi^2(5)= 14.20$, $p<.05$). There were no differences in the anxiety scores or the ethnicity between the families who agreed to take part and those who did not.

Zygosity was established using parent-report questionnaires. This method is estimated to be over 95% accurate (Goldsmith, 1991; Price et al., 2000). Where zygosity was ambiguous (5% of the sample), DNA was collected from cheek swabs in order to assign zygosity. At wave 1 the sample consisted of 100 monozygotic, 82 same-sex dizygotic, 117 opposite-sex dizygotic twin pairs and one twin pair of unknown zygosity who did not consent to zygosity clarification using the DNA method. At wave 2 the sample consisted of 83 monozygotic, 69 same-sex dizygotic and 98 opposite-sex dizygotic twin pairs. There were slightly more females than males in the sample at both waves (169.5 twin pairs (57%) at wave 1 and 141 twin pairs (65%) at wave 2 were female). The majority of twin pairs were White (N = 256 (87%) at wave 1, N = 220 (88%) at wave 2), which was comparable to the national average (Scott, Pearce, & Goldblatt, 2001). The majority of parents remained in education until 18 years (mothers: N=157, 54%, fathers: N=175, 61%) and were employed (mothers: N=215, 74%, fathers: N=269, 93%). These are in line with the national statistics (Ward, 2013).

Data collection was conducted at the Institute of Psychiatry, King's College London, United Kingdom, apart from a small number of children who were visited in their homes. At both time points, the testing session was approximately two hours long and consisted of questionnaires and experimental paradigms, with a break half way through. Twins completed the two halves of the testing in the opposite order to one another to counter-balance any practice or fatigue

effects. Parents of twins completed a range of questionnaires in a separate room. The task order was counterbalanced across families.

In order to generalise the results from this selected sample to the whole population, a weight was incorporated into all analyses. The weight controls for biases due to ascertainment – i.e. oversampling symptomatic children. The weight used the ratio of the selection probability of high symptom families to that of non-symptomatic families to control for bias associated with ascertainment across waves, and the inverse of the predicted probability of families remaining at wave 2 to control for bias associated with attrition. In short, lower weights were assigned to individuals from categories over-represented in the sample, and higher weights to individuals from categories under-represented in the sample relative to the population distribution. The weights were designed to be family-general, such that in model-fitting analyses, the weights did not incur any additional individual-specific effects between the members of the same family. The weight did not change the results in a way that would alter the interpretation (Lau, Gregory, Goldwin, Pine, & Eley, 2007).

2.2.2. ADOLESCENT AND YOUNG ADULT TWIN AND SIBLING SAMPLE: G1219

The Genesis 12-19 (G1219) twin study is a longitudinal sample of 3,640 twin and sibling pairs aged between 12 and 19 at initial contact. It is an ongoing study and to date consists of five waves of data collection via questionnaires sent to the participants over a thirteen year period. Questionnaires were also sent to the parents at waves 1 and 3 of data collection. For all waves, informed consent was obtained from parents/guardians of all participating adolescents under 16 and from participants themselves when over 16. The study was granted ethical approval by the Research Ethics Committees of the Institute of Psychiatry, South London and Maudsley NHS Trust for all waves, and Goldsmiths, University of London for waves 4 and 5. The

recruitment details and sample characteristics are described in McAdams et al. (2013). Chapters 3, 4 and 5 of this thesis use the waves 2-4 of the G1219 study.

The G1219 participants were recruited using two strategies. First, the twin pairs were recruited in collaboration with the UK Office of National Statistics. The health authorities and general practitioners contacted 2,947 families with twins born between 1985 and 1988 on the behalf of the G1219 team. Of these, 1,381 (47%) twin pairs agreed to participate. Second, the sibling pairs were recruited from the GENESiS study (Sham et al., 2000), a large study of approximately 40,000 adults, of whom approximately 9,000 indicated that they had children living with them. These families were contacted to take part in G1219 if they had children aged 12-19. A total of 1,294 families responded, of whom 1,747 adolescents from 1,241 families were aged 12-19. This sample included 445 sibling pairs, with a mean average age difference of 28 months, and a maximum age difference of 70 months.

The five years at which the data collection took place for the G1219 waves 1-5 were 2000, 2001, 2003, 2007 and 2012 respectively. The present analyses focus on the waves 2-4 of the data collection. The sample size and other participant characteristics at these three waves are presented in Table 2.1. Participants were on average 15, 17 and 20 years old at these three waves. Zygosity was established using parent-report questionnaires assessing the physical similarity between pairs. This method is estimated to be over 95% accurate (Goldsmith, 1991; Price et al., 2000). When there was disagreement between zygosity ratings between wave one and two, DNA was obtained (N=26 pairs) before final classifications were made. There were more females than males in the study.

Table 2.1 - Sample characteristics for G1219 study waves 2-4

	Wave 2	Wave 3	Wave 4
N (pairs)	1,372	866	896
Female/Male pairs (%)	768 (56) / 604 (44)	520 (60) /346 (40)	547 (61) / 349 (39)
Age: Mean (years, months) (range)	15,0 (12,0 – 21,0)	17,0 (14,0 – 23,0)	20,0 (18,0 – 27,0)
Zygosity (MZ/DZS/DZO/Sib/Unknown)	350/313/334/330/45	234/207/232/182/11	230/214/232/201/19

Note. The inclusion of siblings inevitably resulted in large age ranges; however the majority of the participants were twins with a tighter age range (e.g. at wave 3, age SD=1.11, range=15-19 for twins, age SD=1.97, range=14-23 for siblings).

The representativeness of the G1219 families has been assessed by comparing the wave 1 demographic variables to those detailed in a large survey carried out on a nationally representative sample of parents in the UK in 1999 (Meltzer, Gatward, Goodman, & Ford, 2000). Parental education level in the G1219 participants was slightly higher than the population based sample, with 39% educated to A-level or above compared to 32% in the nationally representative sample. Parents from the G1219 sample were also more likely to own their own homes (82% compared to 68% in the nationally representative sample). The attrition was predicted by parental education (responses were more likely from individuals with parents reporting higher qualifications), housing tenure (responses were more likely from parents reporting home ownership), delinquency (averaged across siblings, responses more likely from less delinquent participants) and child sex (girls being more likely than boys to remain in the study).

2.2.3. ADOLESCENT TWIN SAMPLE: TEDS

The Twins Early Development Study (TEDS) is a large and ongoing longitudinal study of over 10,000 twin pairs born in England and Wales in 1994, 1995, and 1996. The participants were identified through birth records and contacted by the UK Office for National Statistics on the behalf of the TEDS team. Of these, 16,810 responded to acknowledge their interest in participating in the study and 13,694 (81%) returned questionnaires at the first contact when the twins were 18 months old. These families have been invited to take part in studies at multiple ages throughout childhood and adolescence, with the most recent wave of data collected when twins were 18 years old. The families in the TEDS sample are representative of the general UK population. In adolescence, about 93% were White, which is comparable to the national average (Scott et al., 2001). Forty percent of parents had A-level or higher education qualifications, and 46% of mothers and 93% of fathers were employed, which is comparable to the national estimates (Meltzer et al., 2000). Full recruitment details and the most up to date information about all the waves of data collection are provided in Haworth, Davis, and Plomin (2013).

The current analyses focus on the data collected when twins were approximately 16 years old (mean age=16.32, SD=.68 years). The data collection took place in 2011. Informed consent was obtained from parents of all participating adolescents and the study was approved by the Institute of Psychiatry Ethics Committee. Zygosity was established using parent-report questionnaires of physical similarity, which is estimated to be 95% accurate when compared to DNA testing (Price et al., 2000). Where zygosity was ambiguous, DNA testing was conducted. Initial contact by mail was attempted for 10,868 families of the original 16,810 cohort. Of the 5,942 families that were not contacted, roughly 1620 had withdrawn, roughly 2270 were inactive (no previous data returned), roughly 1850 had address problems and the remainder

(roughly 200) were medical exclusions or other special cases. The questionnaire booklets were returned by 10,320 individuals (47.1% response rate). Of these, 56% were female, 35% monozygotic, 33% same-sex dizygotic and 32% opposite-sex dizygotic twins. Participants were excluded from the analyses if they did not provide consent, if they had severe medical disorders, experienced severe perinatal complications or if their zygosity was unknown (N=316 families).

2.2.4. UNSELECTED CHILD SAMPLE: ATTENTIONAL CONTROL STUDY

The Attentional Control study is a one wave school-based experimental study of primary school children. Ethical approval was granted by the Psychiatry, Nursing and Midwifery Research Ethics Subcommittee of King's College London (ref no: PNM/12/13-54). Participants in the Attentional Control study were recruited from a primary school in Dulwich Village, London, UK. The school was recruited based on the geographical proximity to the Institute of Psychiatry, London. Parents of all children aged 8-10 years in the school were sent an information sheet, brief family background questionnaire and consent form. Written consent was obtained from parents, as well as verbal assent from the participating children. Sixty-one children (mean age=9.23 years, SD=.57, range: 8.39-10.41) participated (34% response rate). Out of these 52% were male, 95% right-handed and 90% classified as Caucasian, which is comparable to the UK general population (Scott et al., 2001).

Children were supervised by a researcher during a 1 hour testing session undertaken individually in a quiet classroom during the school hours. The tasks were displayed on a laptop (13.3'' display with 16:9 aspect ratio) and each image was size 130×178 pixels. All tasks were programmed in E-Prime 2.0 (Psychology Software Tools, Pittsburgh, PA). Instructions and questionnaire items were read aloud to ensure comprehension. The questionnaires were completed first in a randomised order, followed by the three experimental tasks. For

comparison with other published studies, the shapes task was always completed first, to prevent introducing potential carry over effects of the face task. The four blocks of face tasks were presented next, in a randomised order. Children were instructed to press a button on a keyboard (L for 'horizontal', A for 'vertical', both labelled clearly) to indicate whether the line segment belonging to the target shape or face was horizontally or vertically oriented. In accordance with previous research using the irrelevant singleton task (Moser et al., 2012), they were instructed to ignore any colour/facial expression information and focus solely on finding the odd shape/gender face. Reaction time on experimental tasks was recorded. Across the three tasks participants completed 480 trials in total, with breaks in-between blocks and tasks. The children and the school each received a voucher for participating.

2.3. MEASURES

The current thesis uses a range of self-report and experimental measures to assess depression, anxiety symptom clusters, cognitive biases and cognitive deficits. An overview of the measures used is presented in Table 2.2. All self-reported measures demonstrated good internal consistencies in the current samples, as presented in Table 2.3.

Table 2.2 - Overview of the measures included in the current thesis

Sample	Wave	Measures			
		Depression	Anxiety	Cognitive: self-report	Cognitive: experimental
ECHO	Wave 1	CDI	SCARED	CASI	-
	Wave 2	CDI	SCARED	CASI	-
G1219	Wave2	SMFQ	SCAS	CASI	-
	Wave 3	SMFQ	SCAS	CASI	-
	Wave 4	SMFQ	RSAS	ASI	-
TEDS		SMFQ	-	CASI, MAAS short	-
The Attentional Control Study		SMFQ	STAIC-T	-	The irrelevant singleton task: shape and face versions

Notes: CDI – the Children's Depression Inventory, SMFQ - the Short Mood and Feelings Questionnaire, SCARED - the Screen for Child Anxiety Related Emotional Disorders, SCAS - the Spence Children's Anxiety Scales, RSAS - the Revised Symptoms of Anxiety Scale, STAIC-T - the Trait Anxiety Inventory for Children, (C)ASI – the (Childhood) Anxiety Sensitivity Index, MAAS short - the short version of the Mindful Attention Awareness Scale.

Table 2.3 - Internal consistencies of the self-report measures in the current thesis

Sample	Measure	Wave		
		1	2	3
ECHO	CDI	.81	.81	-
	SCARED	.88	.90	-
	CASI	.80	.80	-
G1219	SMFQ	.86	.79	.90
	SCAS/ RSAS	.88	.87	.94
	CASI/ASI	.82	.86	.89
TEDS	SMFQ	.88	-	-
	CASI	.86	-	-
	MAAS short	.76	-	-
The Attentional Control Study	SMFQ	.81	-	-
	STAIC-T	.85	-	-

Notes: CDI – the Children's Depression Inventory, SMFQ - the Short Mood and Feelings Questionnaire, SCARED - the Screen for Child Anxiety Related Emotional Disorders, SCAS - the Spence Children's Anxiety Scales, RSAS - the Revised Symptoms of Anxiety Scale, STAIC-T - the Trait Anxiety Inventory for Children, (C)ASI – the (Childhood) Anxiety Sensitivity Index, MAAS short – the short version of the Mindful Attention Awareness Scale.

2.3.1. DEPRESSION

Both waves of the ECHO twin study used the Children's Depression Inventory (CDI) (Kovacs, 1985) to assess depression. The CDI is a 27-item self-report questionnaire that examines affective, cognitive and behavioural signs of current depression. Children indicated which statement applied to them in the last two weeks (e.g. "I feel like crying once in a while", "I feel like crying many days", "I feel like crying every day"). Responses are summed across all items to create total depression score. The measure demonstrates good reliability and validity (Kovacs, 1985).

In the remaining samples depression symptoms were measured using the Short Mood and Feelings Questionnaire (SMFQ) (Angold et al., 1995). It is a 13-item self-report measure assessing whether (not true, sometimes, true) symptoms of depression occurred in the previous two weeks. Responses are summed across all items to create total depression score. The SMFQ has sound psychometric properties (Angold et al., 1995), can discriminate between the individuals with depression and healthy controls (Burleson Daviss et al., 2006; Rhew et al., 2010), and is suitable for research with children as well as adolescents (Angold et al., 1995; Brooks & Kutcher, 2001).

2.3.2. ANXIETY

Anxiety symptom clusters were measured using a range of self-report questionnaires suitable to the age of the participants being studied. Both waves of the ECHO twin study used the Screen for Child Anxiety Related Emotional Disorders (SCARED) (Birmaher et al., 1999). The SCARED contains 41 self-report items that assess anxiety using the then current DSM-IV criteria. Children indicated how often (almost never, sometimes, often) in the last 3 months

they experienced the anxiety disorder symptoms. The SCARED can be summed to create a total anxiety score, as well as five DSM-IV-related anxiety subscale scores: generalized anxiety, panic/somatic symptoms, separation anxiety, social anxiety and school phobia. In the current thesis, four subscale scores were used in chapters 3 and 4 (school anxiety was excluded for consistency with the measures used in the older group, where school anxiety was not assessed). The total anxiety score was used in chapter 5. The SCARED has sound psychometric properties (Birmaher et al., 1999; Monga et al., 2000).

In the G1219 twin study, two separate anxiety measures were used to capture adolescent anxiety disorder symptoms (waves 2 and 3) as well as the anxiety symptoms in young adulthood (wave 4). At waves 2 and 3, the Spence Children's Anxiety Scales (SCAS) (Spence, 1998) were used. Adolescents indicated the frequency (never, sometimes, often, always) of experiencing a range of anxiety disorder symptoms on a 38 self-report item scale. The SCAS can be summed to create a total anxiety score, as well as six anxiety subscale scores: generalized anxiety, panic, separation anxiety, social anxiety, fear of physical injury and OCD. In the current thesis, four subscale scores were used in chapters 3 and 4 (fear of physical injury and OCD were excluded for consistency with the measures used in the ECHO sample). The total anxiety score was used in chapter 5. The SCAS has sound psychometric properties in adolescents (Muris, Merckelbach, Ollendick, King, & Bogie, 2002), it discriminates well between children with clinical anxiety versus healthy controls and shows good convergent validity with other anxiety measures (Spence, 1998).

At G1219 wave 4 the Revised Symptoms of Anxiety Scale (RSAS) (Willis, Day, Eley, Chorpita, & Gregory, Unpublished) was used to measure anxiety symptoms. It is an age-appropriate version of the Revised Child Anxiety and Depression Scale (RCADS) (Chorpita, Yim, Moffitt, Umemoto, & Francis, 2000), which is itself a revised version of the SCAS questionnaire used in the earlier waves. It is a well-validated questionnaire of common childhood anxiety and depression symptoms (Muris et al., 2002). For the RSAS, the anxiety items from the RCADS

were adapted by a group of three psychologists with experience in anxiety research to make the items more appropriate for adult participants. For example, the questions assessing school-related worries were modified to assess work-related concerns instead. The RSAS consists of 36 self-report items designed to assess the DSM-IV anxiety disorder symptoms. The responders were asked to rate how often (never, sometimes, often, always) they experienced each item. The RSAS can be summed to create a total anxiety score, as well as five subscale scores: generalized anxiety, panic, separation anxiety, social anxiety and OCD. In the current thesis, four subscale scores were used in chapters 3 and 4 (OCD was excluded in the interest of consistency because it was not measured in the younger group), while the total anxiety score was used in chapter 5.

In the Attentional Control study, trait anxiety was assessed using the Trait Anxiety Inventory for Children (STAIC-T) (Spielberger, 1973). Children were asked to indicate how often (hardly ever, sometimes, often) the 20 questionnaire items were true for them. The responses can be summed to create a total trait anxiety score. The psychometric properties of STAIC-T are very good (Finch Jr, Montgomery, & Deardorff, 1974; Papay & Hedl Jr, 1978).

2.3.3. SELF-REPORTED COGNITIVE PROCESSES

Anxiety sensitivity was measured at G1219 waves 2 and 3, and in TEDS using the Childhood Anxiety Sensitivity Index (CASI) (Silverman, Fleisig, Rabian, & Peterson, 1991). The CASI contains 18 self-report items that assess the fear of anxiety sensations in young people. Participants are required to indicate on a three-point Likert scale (1=none to 3=a lot) how much the statements about the perceptions of their anxiety symptoms (e.g. “It scares me when my heart beats fast”) are true about them. At G1219 wave 4, anxiety sensitivity was measured using the adult version of the CASI, the Anxiety Sensitivity Index (ASI) (Reiss et al.,

1986). The only differences between the two scales are the simplicity of the language used, the number of items (the ASI contains 16 items, the excluded items are "Funny feelings in my body scare me" and "I don't like to let my feelings show"), and the response scale (the ASI uses a five point Likert scale, where 1=very little to 5=very much). The CASI and ASI can be summed to create a total anxiety sensitivity score, as well as three anxiety sensitivity subscales: physical, social and mental concerns. These subscales are created based on the previous factor analyses in the G1219 study (Brown et al., 2012). In the current thesis, the three subscale scores were used in chapter 5 and the total anxiety sensitivity score was used in chapter 6. The psychometric properties of both measures are very good (Peterson & Plehn, 1999; Silverman et al., 1991).

Mindfulness was measured in TEDS using a short version (Van Dam, Earleywine, & Borders, 2010) of the Mindful Attention Awareness Scale (MAAS) (Brown & Ryan, 2003). Van Dam et al. (2010) conducted an item response theory analyses of the total MAAS scale and concluded that only five items confer the majority of statistical information about the underlying latent mindfulness trait and are able to discriminate between individuals of varying levels of the mindfulness. The 5 self-report items focus on the statements relating to attentional control (e.g., "I find myself doing things without paying attention"). Participants respond on a 6-point Likert scale (from "almost always" to "almost never") to indicate how often they have these experiences. The responses are summed to create a total mindfulness score; the higher score reflects lower mindfulness level. Psychometric studies corroborate the utility of the short version of the MAAS scale in adolescence (Black, Sussman, Johnson, & Milam, 2012).

2.3.4. COGNITIVE EXPERIMENTAL TASKS

Three versions of a visual search paradigm were used to examine the attentional cognitive biases and deficits in the Attentional Control study. Across the three tasks, the emotional value of the items in the visual search array was manipulated in order to directly compare how neutral and emotional information influence attentional control. Two neutral (*shapes task* and *faces-colour task*) versus one emotional (*faces-valence task*) version of the task were used. The tasks are described in detail in chapter 7.

The visual search task is based on the irrelevant singleton method (Theeuwes, 1991, 1992). In this method participants perform a visual search for a target odd shape in an array of shapes, and on 50% of the trials a salient, task-irrelevant colour distractor is present. The slower reaction time caused by the presence of a distractor, relative to the no-distractor trials, indexes the amount of attentional capture via the bottom-up system, providing a direct measure of the inhibitory top-down attentional control (Theeuwes, 2010). First, in the *shapes task* participants are required to find the odd shape (e.g. green circle) in the visual search array (e.g. nine green diamonds) and to identify whether the line inside the odd shape was horizontal or vertical. On a distractor trial one of the shapes in the array is of opposite colour (e.g. one red diamond). This task is a standard measure of attentional control used previously in adults (Esterman et al., 2013; Moser et al., 2012).

The *faces-colour task* is a novel adaptation of the shapes task that measures attentional capture by an irrelevant colour singleton using face stimuli instead of shapes. Participants are required to find the odd gender face in the array (e.g. one green female face in the array of green male faces), and identify whether the line next to the odd gender face is horizontal or vertical. On the distractor trials (50% of all trials) one face in the array appears in the opposite colour (e.g. red male face). A slower reaction time on trials when the colour distractor face is present indicates the degree of attentional capture. Finally, the aim of the *faces-valence task* is

to measure the attentional capture by an irrelevant *emotional* distractor amongst an array of face stimuli. In this task, participants are again required to identify whether the line next to the odd gender face is horizontal or vertical. However, instead of the presence of the colour-face distractor, there is a facial expression distractor. On the no-distractor trials (50% of all the trials), all 10 faces share the same facial expression (either neutral or angry). The distractor trials are identical, but one of the nine non-target faces is randomly selected to appear in the opposite facial expression to the other faces. For example, if nine faces have a neutral expression (eight identical female faces and one target male face, all the same colour), the distractor face has an angry expression (an angry female face of the same identity and colour as the remaining neutral female faces). A slower reaction time on trials when the emotional distractor face is present indicates the degree of attentional bias. The direct comparison between the performance on the faces-colour and faces-valence task allows us to assess whether the magnitude of attentional capture by an emotional distractor (attentional bias) differs from the attentional capture by a neutral, colour distractor (attentional control).

2.4. TWIN METHODOLOGY

The aim of the twin design is to study the relative contribution of the genetic and environmental influences to individual differences in traits. This method takes advantage of the known genetic differences between the two naturally existing types of twins: monozygotic (MZ) and dizygotic (DZ) twins. This section outlines the principles and genetic models of the twin methodology. For more detailed description, see Rijsdijk and Sham (2002) as well as Plomin et al. (2013).

2.4.1. UNIVARIATE ANALYSIS

The classical twin design compares the degree of similarity between MZ (sharing 100% of the genes) and DZ (sharing on average 50% of their genes) twin pairs. This information allows disentangling four sources of influences on individual differences in traits. First, additive genetic influences (A) represent the sum of the effects of the individual alleles at all loci that influence the trait, i.e. it indexes the *heritability* of a trait. Second, non-additive genetic influences (D) capture the interactions between alleles at the same (dominance) or different (epistasis) loci, and unlike A these genetic influences are not transmitted from parents to offspring. Third, shared environmental influences (C) are the environmental influences that make individuals in the family more similar to each other. Finally, non-shared environmental influences (E) are the environmental influences that make individuals in the family different from each other. Of note, the parameter also contains measurement error. It is also important to note that the terms *shared* and *non-shared* refer to the way in which the environment affects twins within a pair. For example, a specific event such as parental divorce can have both shared and non-shared influences on the twins. These different influences combine to make the total phenotypic variance (V_p = A + D + C + E). The relative contribution of each of the variance components is estimated by comparing the MZ and DZ correlations on a given trait (i.e. the cross-twin within-trait covariances - how the score of twin 1 on trait 1 correlates with the score of twin 2 on trait 1, denoted r_{MZ} and r_{DZ} for each twin type respectively). Thus, these aetiological influences are considered 'latent', as they are inferred and not measured directly.

MZ twins share the same A, C and D influences. DZ twins share all of their C influences, only half of the A influences and a quarter of the D influences. By definition both types of twins do not share any of their E influences. As there are only three predictive statistics (r_{MZ}, r_{DZ} and V_p), C and D cannot be estimated simultaneously in a model, thus only three sources of influence can be estimated at the same time - either ACE or ADE. The relative magnitudes of the twin

correlations can be used to indicate whether C or D is more likely to be present – if the r_{DZ} is more than half the size of the r_{MZ}, this indicates that C is present. If the r_{DZ} is smaller than half the size of the r_{MZ}, this indicates that D is present because D correlates perfectly for MZ twins while only 25% for DZ twins. Dominance is rarely seen in twin studies of anxiety and depression in young people and is not seen in any of the analyses presented in this thesis, therefore it is not discussed further.

Focusing on the ACE model, the relative contributions of each of these influences can be calculated using Falconer's formulas. First, assuming that MZ twins are not treated more similarly than DZ twins (equal environment assumption, see section 2.4.5), any excess similarity between MZ and DZ correlations indicates additive genetic influences because MZ twins share all their genes, while DZ twins share on average only half of the additive genetic influences. A influences can be calculated using the following formula:

$A=2(r_{MZ}-r_{DZ})$

Second, an estimate of C is given by the difference in the MZ correlations and the estimated genetic influences. C influences can be calculated using the following formula:

$C=rMZ-A$, or $C=2r_{DZ}-r_{MZ}$

Finally, if the MZ correlations are less than 1, the remaining variance can only be explained by the E influences on the trait, as it is the only influence that can make the MZ twins different from each other. E influences can be calculated using the following formula:

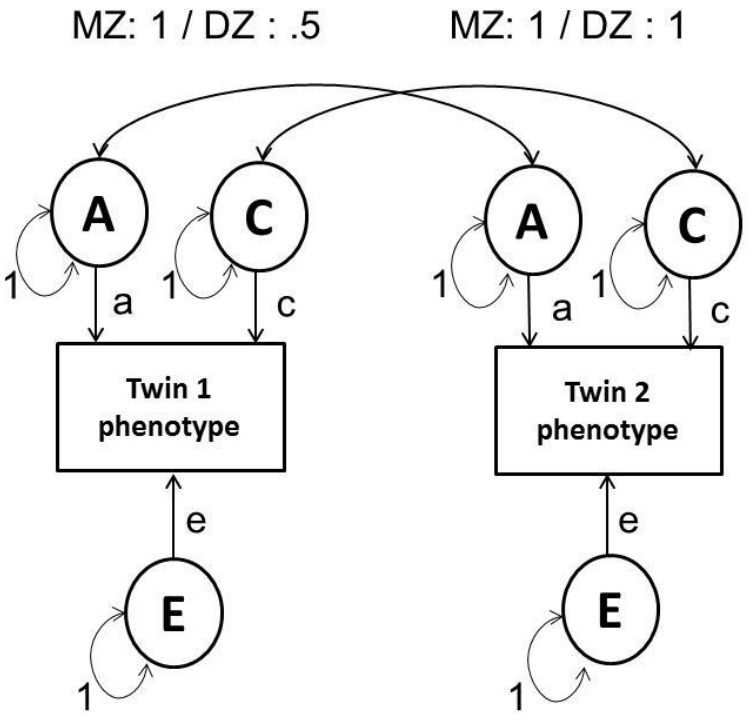
$E= 1-r_{MZ}$ or $E=1-(A+C)$

Path diagrams are a convenient technique that allows analysis of the linear relationships between the variables and also enables the predictions for the variances and covariances under the specified model (Wright, 1921). The full ACE univariate twin model is presented in

Figure 2.1. The observed variables are represented by rectangles (e.g. the phenotype), the latent variables are presented in circles (e.g. inferred A, C and E influences), the causal paths are presented by single-headed arrows (e.g. the path 'a' represents the genetic influences on the phenotype) and the covariance paths are presented by the curved double-headed arrows (e.g. the correlation between the genetic influences in twin 1 and twin 2). Path tracing rules state that the covariance between any two variables is the sum of all legitimate chains connecting the variables. The numerical value of a chain is the product of all traced path coefficients in it. A legitimate chain is a path along arrows that follows three rules. First, it is allowed to either trace backwards, then forward, or simply forwards, from variable to variable. Second, it is not allowed to trace twice through the same variable. Third, there can only be a maximum of one bi-directional path per chain.

The variance of the variable is the covariance of the variable with itself, thus the expected variance is the sum of all paths from the variable to itself. Using the path tracing rules, the total variance of twin 1 phenotype is $a\times1\times a + c\times1\times c + e\times1\times e = a^2+c^2+e^2$. The total covariance between twin 1 and twin 2 phenotypes is the sum of all legitimate connections between these observed variables: $a\times1\times a + c\times1\times c = a^2+c^2$ for MZ twin pairs, and $a\times.5\times a + c\times1\times c = .5a^2+c^2$ for DZ twin pairs.

Figure 2.1 - Path diagram for the univariate ACE model



Notes: A – additive genetic influences, C – shared environmental influences, E – non-shared environmental influences.

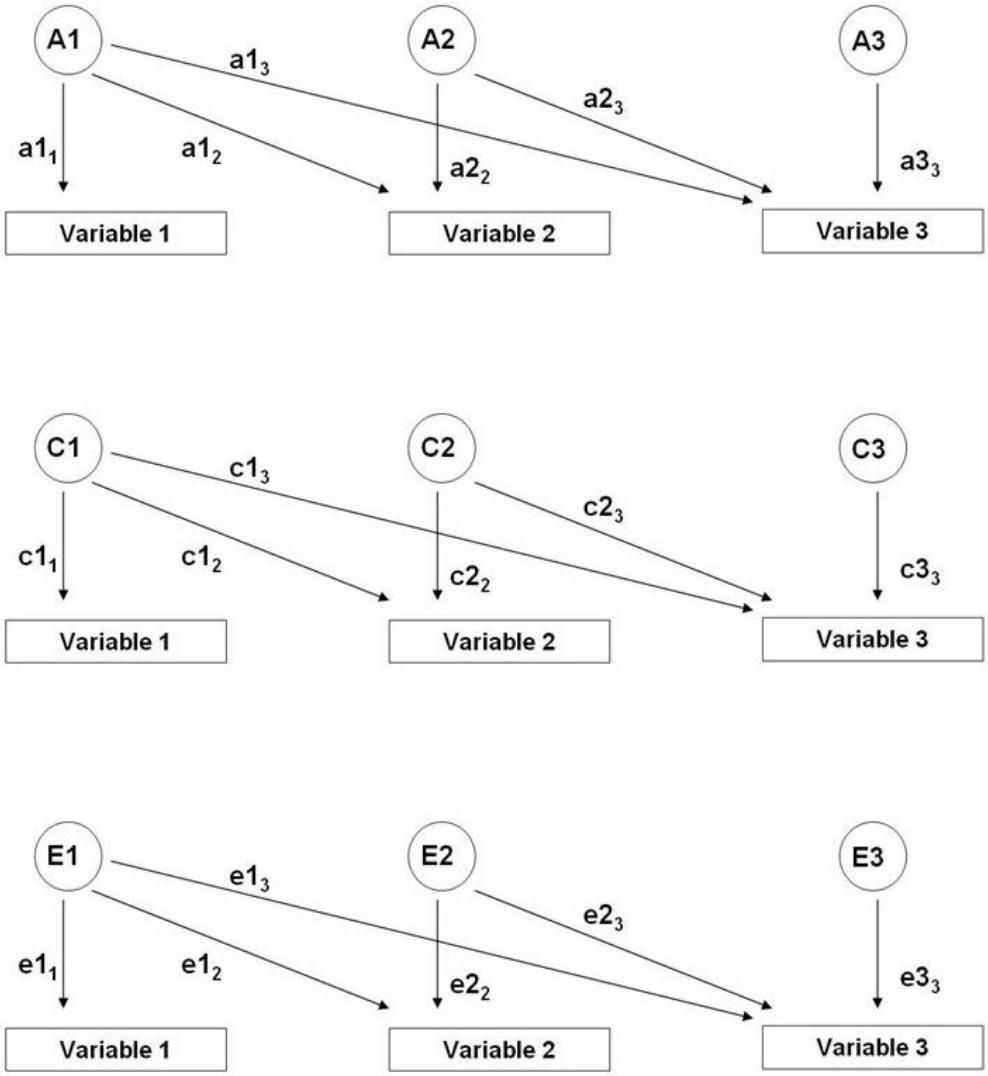
2.4.2. MULTIVARIATE ANALYSIS

The model fitting approach can be extended to the analyses of the genetic and environmental influences on multiple traits that have been measured in twin pairs. The relative contribution of A, C and E to the covariance between two or more different traits is estimated by comparing the MZ and DZ correlations across these traits (i.e. the cross-twin cross-trait covariances - how the score of twin 1 on trait 1 correlates with the score of twin 2 on trait 2). The different traits can be separate measures, but they can also be the same measure collected at multiple time points or from multiple informants. Multivariate analyses can be used to address several research questions, such as the degree of the genetic and environmental overlap between

different variables, the amount of the phenotypic correlation between the traits that is due to genetic versus environmental influences, and the higher order latent structure of the genetic and environmental influences on the variables.

There are three most commonly used multivariate twin models that differ in the way in which the genetic and environmental influences are assumed to influence the variables. First, the least parsimonious of these models is the *Cholesky decomposition*. A trivariate Cholesky decomposition is illustrated in Figure 2.2. It assumes three distinct sets of genetic and environmental influences on each variable. A1, C1 and E1 are influences on the first variable via paths a11, c11 and e11 that can also influence the remaining two variables via paths a12, a13, c12, c13, e12 and e13. A2, C2 and E2 influence the second variable via paths a22, c22 and e22 and can also influence the third variable via paths a23, c23 and e23, over and above the influences accounted for by A1, C1 and E1. Finally, A3, C3 and E3 are specific influences unique to the third variable only (via paths a33, c33 and e33). Total A, C and E effects on each individual measure can be obtained by summing all paths to that measure (e.g. total genetic influences on the third variable can be obtained by adding influences from paths a13, a23 and a33). Thus, the Cholesky decomposition allows us to estimate the extent to which aetiological factors influencing the variables earlier in the sequence also influence the variables further in the sequence, and for this reason is especially useful for longitudinal data. The Cholesky decomposition was used in chapters 4 and 6 of this thesis.

Figure 2.2 - Cholesky decomposition

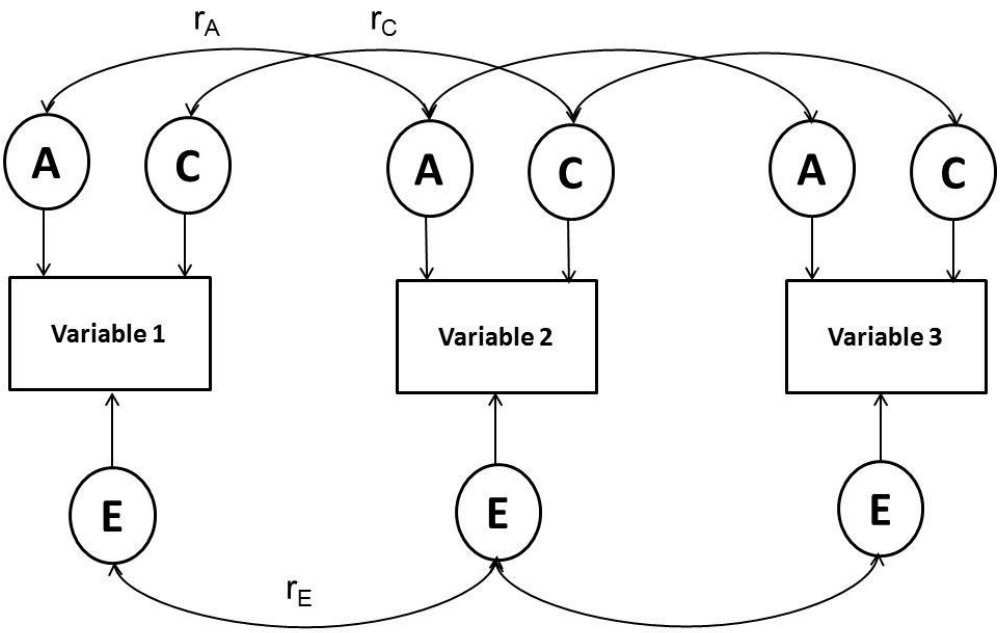


Notes: A – additive genetic influences, C – shared environmental influences, E – non-shared environmental influences.

The path diagram depicts only one member of the twin pair.

The Cholesky decomposition can be represented as a *correlated factors solution* (Figure 2.3). The correlated factors solution estimates the degree of the genetic and environmental overlap between each pair of the variables, and makes no assumption about the higher order structure of the aetiological influences. The correlated factors solution assumes that each variable has unique A, C and E influences. These trait-specific influences are allowed to correlate with the A, C and E influences on other traits (r_A=genetic correlation, r_C=shared environmental correlation and r_E=non-shared environmental correlation). The proportion of the phenotypic correlations accounted for by A, C and E influences can also be calculated by standardizing variance components. The correlated factors solution was used in chapters 3, 5 and 6 of this thesis.

Figure 2.3 - Correlated factors solution

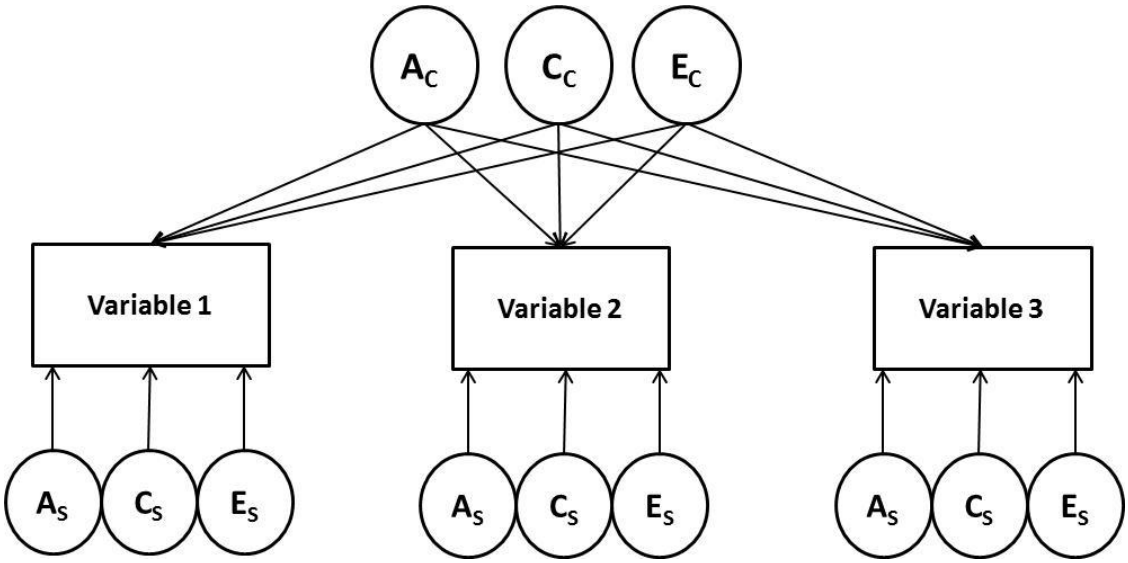


Notes: A – additive genetic influences, C – shared environmental influences, E – non-shared environmental influences, r_A – genetic correlation, r_C – shared environmental correlation, r_E – non-shared environmental correlation.

The path diagram depicts only one member of the twin pair.

The *independent pathways model* is illustrated in Figure 2.4. The model allows a set of common (A_C, C_C and E_C) and variable-specific (A_S, C_S and E_S) genetic and environmental influences on each variable directly. Common influences account for the between traits covariance, while variable-specific influences account for variance that is not shared with other traits. The model tests whether there are common etiological factors that influence the variables, in addition to the variable-specific factors. In order for an unconstrained independents pathways model to be identified, each higher order factor needs to load on at least three measured variables (Rijsdijk, 2005b). The independent pathways model was used in chapter 3 of this thesis.

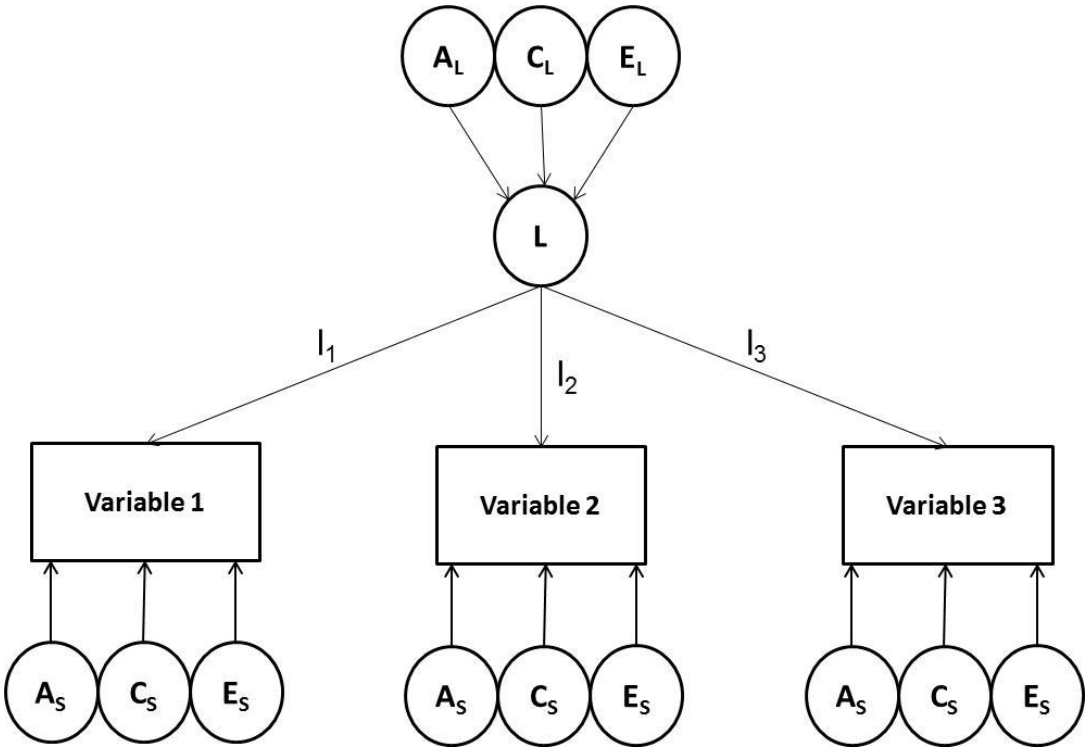
Figure 2.4 - Independent pathways model



Notes: A – additive genetic influences, C – shared environmental influences, E – non-shared environmental influences. Subscript 'c' denotes influences common to all variables, subscript 's' denotes variable-specific influences. The path diagram depicts only one member of the twin pair.

Finally, the most parsimonious of the models, the *common pathways model*, is illustrated in Figure 2.5. This model assumes a higher order latent factor (L) that influences the variables. There are also variable-specific genetic and environmental influences (A_S, C_S and E_S). Variance of the latent factor can be decomposed into genetic (A_L) and environmental (C_L and E_L) influences. Of note, E_L is free from variable-specific measurement error (which is captured by E_S) but not from shared measurement error. Thus, the common pathways model estimates the aetiology of the latent trait, as well as the relative contributions of this latent trait (via paths l_1, l_2 and l_3) to the measured variables, in addition to relative contributions of variable-specific factors. In order for an unconstrained common pathways model to be identified, each higher order factor needs to load on at least three measured variables (Rijsdijk, 2005a). The common pathways model was used in chapter 4 of this thesis.

Figure 2.5 - Common pathways model



Notes: L – latent factor, A – additive genetic influences, C – shared environmental influences, E – non-shared environmental influences. Subscript 'L' denotes influences that act on the variables via the latent factor, subscript 'S' denotes variable-specific influences.

The path diagram depicts only one member of the twin pair.

2.4.3. SEX DIFFERENCES

The sex differences in the aetiological influences on a trait can be examined using twin modelling. There are three types of sex differences that can be examined. First, *qualitative sex differences* test whether the same genetic and environmental sources contribute to individual differences in the phenotype for males and females. The DZ opposite-sex twins are necessary for testing for qualitative sex differences, as the models test whether the genetic and shared

environmental correlation between the twin 1 (male) and twin 2 (female) can be fixed to .5 and 1 respectively. Second, the *quantitative sex differences* test whether the same genetic and environmental sources influence the trait in males and females to different degree. This is assessed by testing whether fitting a single set of A, C and E influences deteriorates the model fit when compared to the less parsimonious model that assumes estimates of different magnitudes of A, C and E influences in males and females. If qualitative or quantitative sex differences are found, the A, C and E influences should be estimated separately for males and females. Finally, the *scalar sex differences* model investigates whether there is a difference in the magnitude of variance between males and females, i.e. it tests whether males and females show the same scores distribution on a particular trait. If scalar sex differences are detected, a scalar variable is added to the model to correct for the difference in variances between males and females, and a single set of A, C and E estimates is obtained. Testing sex differences requires large sample size to be adequately powered. For this reason it has only been conducted in G1219 and TEDS samples in this thesis.

2.4.4. MODEL SELECTION

"*Everything should be made as simple as possible, but not simpler"* is a quote attributed to Albert Einstein and it illustrates the principle of parsimony. The principle posits that among the competing models that predict the data equally well, the model that has the fewest number of parameters should be selected. However, the model cannot be oversimplified to the point that its predictive ability significantly reduces. The aim of the model comparison is therefore to test whether a simpler, more parsimonious model fits the data as well as a more complex model, and if it does, this simpler model should be chosen. The saturated model is a model which fully describes data using the maximum number of free parameters, estimating variances, covariances and means for the raw data. The saturated model provides a baseline index of fit

to which more constrained models can be compared. It is also possible to compare two nested (one model can be obtained by simplifying the other model, for example by removing a parameter or applying a constraint) models to each other, for example when testing whether the AE submodel fits significantly worse that the full ACE model, which is done when investigating whether C can be dropped from the model without leading to a deterioration in fit. It is also possible to compare non-nested models to each other, such as when directly comparing the independent and common pathway model to test which one describes the data better.

The OpenMx programme (Boker et al., 2011) which runs within R (www.R-project.org) (TeamRDC, 2010) is one of the most commonly used statistical software designed for analysing genetically sensitive data that controls for non-independence of family members. This statistical package has been used to analyse twin data in the current thesis. It combines matrix algebra of the variance-covariance observed in the data and the assumptions of the twin design, and uses the raw data maximum-likelihood estimation modelling. The core fit statistic used in Open Mx for raw data modelling is minus twice the log likelihood (-2LL) of the observations. The differences in -2LL between models are distributed as χ^2 and the fit of each sub-model can be assessed by the χ2 difference tests. The test compares the fit between the observed covariance matrix and the model covariance matrix and can be used to compare the fit of the nested models. The χ^2 is an absolute fit index that determines how well the a priori model fits the observed data; the lower values indicate better fit. In addition, a range of relative fit indices can be used to compare the models that are not nested, as these fit indices test how well the model fits a hypothesised null model. These include the Akaike's and the Bayesian's Information Criterion (AIC and BIC respectively). The more negative AIC and BIC values indicate better fit. A difference in AIC between two models of 2 or less, provides equivalent support for both models (in which case the most parsimonious model should be chosen), a difference of 3 indicates that the lower AIC model has considerably more support and a difference of more than 10, indicates that the lower AIC model is a substantially better

fit compared to the higher AIC model (Wagenmakers & Farrell, 2004). As conventional in twin modelling, nested and non-nested models are compared against each other to aid model selection, and for this reason Open Mx does not provide other absolute fit indices that use cut-off scores to indicate suitability of the models, such as the Root mean square error of approximation (RMSEA) or the Goodness of fit index (GFI).

Finally, it is important to note that while Open Mx is designed to control for non-independence of family members, phenotypic analyses in other statistical programs were also conducted in a way that accounts for the clustered nature of twin data. Specifically, all phenotypic correlations were conducted using only one randomly assigned twin from each pair. It is crucial to account for the within-pair correlations in order to ensure independence of observations. Non-independent observations are likely to result in too narrow standard errors and incorrectly low p-values, increasing likelihood of Type 1 errors (detecting false positives), and hence increasing the chance of incorrect conclusions.

2.4.5. ASSUMPTIONS AND CONSIDERATIONS

Equal environments assumption

Twin modelling methodology is based on a number of assumptions that need to be considered when interpreting the results. First, it is assumed that the MZ and DZ twin pairs share their environments to the same extent (the equal environments assumption). The implication of violating this assumption and treating the MZ twins as more similar that the DZ twins is that it inflates the MZ correlations relative to the DZ correlations, which results in the overestimation of the genetic influences on a trait. Conversely, if DZ twins are treated more similarly than the MZ twins, this inflates the DZ correlations relatively to the MZ correlations, resulting in the overestimation of the shared environmental influences on a trait.

There are many ways in which both types of twins share their environment to the same degree, for example all twins share their prenatal environment, are raised in the same family environment and are the same age. However, there are also many reasons why the environmental influences on these two twin types can differ. First, twins differ on whether they share the same chorion (protective membrane) during pregnancy, with monochorionic twins experiencing more similar prenatal environment than twins who are dichorionic. A majority of MZ twin pregnancies are monochorionic while all DZ twin pregnancies are dichorionic (Hall, 2003), which results in the MZ twins experiencing more similar prenatal environment than the DZ twins. Second, the MZ twins may be treated more similarly by their parents and other people in their environment, for example due to the increased physical similarity. This hypothesis has been tested by looking at the similarity between the twins whose zygosity was mislabelled. If MZ twins are treated more similarly, then the DZ twins who are mislabelled as MZ twins should be more alike than the DZ twins who were correctly labelled. Conversely, the MZ twins mislabelled as DZ twins should be less alike than the correctly labelled MZ twins. Studies have found little or no effect of labelling on a range of psychiatric traits, including depression and anxiety (Conley, Rauscher, Dawes, Magnusson, & Siegal, 2013; Kendler, Neale, Kessler, Heath, & Eaves, 1993b). Third, MZ twins may have more frequent contact with each other than DZ twins and share more of their childhood experiences and friendship networks, which again could make them more similar to each other. However, the degree of shared experiences does not seem to significantly increase the behavioural or personality similarity between the twins (Borkenau, Riemann, Angleitner, & Spinath, 2002; Plomin, Willerman, & Loehlin, 1976). Furthermore, the studies that compared the similarity in personality of the MZ twins who were reared apart to those who were reared together found that there were no differences in twin resemblance (Bouchard, Lykken, McGue, Segal, & Tellegen, 1990).

It is also important to note that some of the environments can be more similar for DZ than for MZ twins. For example MZ twins are more likely to be allocated to separate classrooms than

DZ twins. Once again, studies have found that these factors are not associated with personality. Furthermore, monochorionic twins, which comprises the majority of MZ twins, are more likely to experience adverse perinatal outcomes than the dichorionic twins (Dube, Dodds, & Armson, 2002; Sebire, Snijders, Hughes, Sepulveda, & Nicolaides, 1997), as well as birth defects (Adegbite, Castille, Ward, & Bajoria, 2004), which could make them more dissimilar. Taken together, the equal environments assumption might not be valid, but the potential bias introduced is thought to be of a very small effect and might have bidirectional influences on the parameter estimates (Felson, 2014).

Gene-environment correlations

The second assumption of twin modelling is that gene-environment correlations and interactions are minimal for the trait. Gene-environment correlation (rGE) reflects the fact that genetic factors can influence the probability of exposure to certain environmental influences. Passive rGE occurs when parents pass both their genes and environments onto their children, such as when anxious parents provide both genetic predisposition to internalizing problems as well as an anxious parenting style (Lau & Eley, 2008b). Active rGE refers to the processes whereby a child's genetically predisposed characteristics evoke certain reactions from others, or when an individual selects and adapts environmental experiences as a function of their genotype. For example, a child with high internalizing problems may be less likely to engage in social activities, which in turn might influence their anxiety and depression levels. Positive active rGE makes MZ twins more alike than DZ twins because the higher genetic resemblance results in higher resemblance in evoked environments, thus inflating genetic parameters. Negative active rGE would have an opposite effect on the genetic estimates. In twin studies, rGE is inferred when genetic influence is found on a measure of environment. One comprehensive systematic review found that all of the investigated environmental influences are heritable (Kendler & Baker, 2007), and there is plenty of evidence for rGE in the internalizing literature (Lau & Eley, 2008b; Rice et al., 2003), indicating that the assumption of

minimal rGE is likely to be violated. However, the effects are likely to act in different directions, possibly cancelling each other out to some degree.

Gene-environment interactions

Gene-environment interaction (G×E) refers to the differential effects of one influence at different levels of another influence. In other words, a specific environmental exposure might have a different impact on an individual depending on their genotype, or a specific genotype may have different influence depending on the presence of a specific environment. The implications of G×E on the variance component estimates depend on the type of the environmental influences the genetic factors interact with (Rijsdijk & Sham, 2002). Genetic interactions with non-shared environmental influences inflate the estimates of the non-shared environmental influences, because they cause both MZ and DZ correlations to decrease. However, genetic interactions with shared environmental influences inflate the estimates of the genetic influences. This is because while both types of twins share their entire shared environment, the MZ twins share more of their genes than the DZ twins, thus there is a higher potential for the interactions in the MZ twins, inflating their resemblance relatively to the DZ twins. G×E has been found to play a role in the internalizing symptoms (Lau et al., 2007; Rice et al., 2006), indicating that the assumption of minimal G×E is probably violated. Again, these effects are likely to influence parameter estimates in different directions, some inflating and some deflating the estimates.

Assortative mating

The third assumption relevant to the twin modelling methodology is that mating in the population occurs at random. However, assortative mating refers to the idea that partner selection might not be random in the population - people might be more likely to have children with individuals who are more or less similar to them (positive and negative assortative mating, respectively). Positive assortative mating would make the partners more

genetically and environmentally similar to each other, which would lead to DZ twins sharing more than 50% of their genetic material on average, resulting in the inflated DZ correlations relative to the MZ correlations. This in turn would lead to the overestimate of the shared environmental influences. The effects are also thought to cumulate across generations. Evidence suggests that positive assortative mating does occur (Boutwell, Beaver, & Barnes, 2012; Eaves, D'Onofrio, & Russell, 1999; Krueger, Moffitt, Caspi, Bleske, & Silva, 1998; Neale & Cardon, 1992), with evidence from a systematic review finding that individuals with affective disorder tends to pair with others who have affective disorder (Mathews & Reus, 2001). However, the impact of the assortative mating on the variance components estimates is thought to be minimal (Maes et al., 1998).

Generalizability to singleton population

Finally, the interpretation of twin modelling results is based on the assumption that twins do not differ from the general population on the measured traits. However, there are several reasons why the results from twins might not be generalizable to the general populations. For example, as mentioned above, the monochorionic pregnancies that characterised most of the MZ twin pregnancies are more likely to have adverse outcomes (Dube et al., 2002; Sebire et al., 1997). Furthermore, twins in general are more likely to be born premature and have lower weight (Rutter & Redshaw, 1991). These problems could affect developmental outcomes, such as behavioural, emotional and cognitive development. However, twins and non-twins are identical in terms of their behavioural and emotional development, educational achievement and personality traits, with the exception of slight language delay (Barnes & Boutwell, 2013; Christensen et al., 2006; Cronk et al., 2002; Johnson, Krueger, Bouchard, & McGue, 2002; Moilanen et al., 1999). Furthermore, these two populations show similar prevalence rates for psychiatric disorders (Simonoff, 1992), although some evidence suggests that twinship might be a protective factor against internalizing symptoms in late childhood (Robbers et al., 2010). Overall the evidence suggests that the results obtained from twin studies are representative of

the general population. Inclusion of siblings in the twin design, as done in the G1219 sample, should increase the generalizability of the results.

The limitations described in this section are likely to have small effects on the variance components estimates. Furthermore, their effects are likely to act in different directions, some will inflate and some will deflate estimates of genetic and environmental influences, possibly cancelling each other out to some degree. Thus, the estimates should always be interpreted as indicative rather than absolute values.

3. CHAPTER 3 - THE PHENOTYPIC AND ETIOLOGICAL STRUCTURE OF DEPRESSION AND ANXIETY DISORDER SYMPTOMS IN CHILDHOOD, ADOLESCENCE AND YOUNG ADULTHOOD.

This chapter is presented as a published paper and is an exact copy of the following journal publication:

Waszczuk, M. A.*, Zavos, H. M. S.*, Gregory, A. M., & Eley, T. C. (2014). The phenotypic and etiological structure of depression and anxiety disorder symptoms in childhood, adolescence and young adulthood. *JAMA Psychiatry, 71*(8), 905-916.

* Joint first authors contributed equally

Supplementary materials for this chapter are presented in **Appendix A**

Original Investigation

The Phenotypic and Genetic Structure of Depression and Anxiety Disorder Symptoms in Childhood, Adolescence, and Young Adulthood

Monika A. Waszczuk, MSc; Helena M. S. Zavos, PhD; Alice M. Gregory, PhD; Thalia C. Eley, PhD

IMPORTANCE The *DSM-5* classifies mood and anxiety disorders as separate conditions. However, some studies in adults find a unidimensional internalizing factor that underpins anxiety and depression, while others support a bidimensional model where symptoms segregate into distress (depression and generalized anxiety) and fear factors (phobia subscales). However, little is known about the phenotypic and genetic structure of internalizing psychopathology in children and adolescents.

OBJECTIVE To investigate the phenotypic associations between depression and anxiety disorder symptom subscales and to test the genetic structures underlying these symptoms (*DSM-5*–related, unidimensional and bidimensional) across 3 developmental stages: childhood, adolescence, and early adulthood.

DESIGN, SETTING, AND PARTICIPANTS Two population-based prospective longitudinal twin/sibling studies conducted in the United Kingdom. The child sample included 578 twins (mean age, approximately 8 and 10 years at waves 1 and 2, respectively). The adolescent and early adulthood sample included 2619 twins/siblings at 3 waves (mean age, 15, 17, and 20 years at each wave).

MAIN OUTCOMES AND MEASURES Self-report symptoms of depression and anxiety disorders.

RESULTS Phenotypically, when controlling for other anxiety subscales, depression symptoms were only associated with generalized anxiety disorder symptoms in childhood (r = 0.20-0.21); this association broadened to panic and social phobia symptoms in adolescence (r = 0.17-0.24 and r = 0.14-0.16, respectively) and all anxiety subscales in young adulthood (r = 0.06-0.19). The genetic associations were in line with phenotypic results. In childhood, anxiety subscales were influenced by a single genetic factor that did not contribute to genetic variance in depression symptoms, suggesting largely independent genetic influences on anxiety and depression. In adolescence, genetic influences were significantly shared between depression and all anxiety subscales in agreement with *DSM-5* conceptualization. In young adulthood, a genetic internalizing factor influencing depression and all anxiety subscales emerged, alongside a small significant genetic fear factor.

CONCLUSIONS AND RELEVANCE These results provide preliminary evidence for different phenotypic and genetic structures of internalizing disorder symptoms in childhood, adolescence, and young adulthood, with depression and anxiety becoming more associated from adolescence. The results inform molecular genetics research and transdiagnostic treatment approaches. The findings affirm the need to continue examining the classification of mood and anxiety disorders in diagnostic systems.

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The publication of the *DSM-5* has been central to the debate regarding the classification of depression and anxiety disorders.[1] Depression and anxiety commonly co-occur[2-4] and are rarely diagnosed in isolation.[2,5,6] They share multiple risk factors[7] including substantial genetic overlap.[8-12] These observations argue against diagnosis-specific etiology of depression and anxiety. However, anxiety is heterogeneous[1] and because of the age changes in internalizing disorders,[5,7,13] it remains unclear whether all anxiety types are equally associated with depression across development.[14-18] To improve diagnostic classification, the current study investigated the etiologic structure of internalizing disorder symptoms in childhood, adolescence, and early adulthood.

Most studies investigating the structure of internalizing disorders and symptoms focus on adults. Some studies provide support for a unidimensional internalizing liability factor that underpins anxiety and depression[6,19-23] in line with evidence of shared genetic effects on several different types of anxiety disorders and depression.[10,24,25] Another influential conceptualization proposes a bidimensional hierarchical model in which generalized anxiety disorder and depression form a distress factor, while the remaining anxiety disorders form a fear factor.[26-30] These 2 factors may be underpinned by separate genetic influences.[31] Importantly, fear and distress are generally highly correlated with each other, thus the 2 conceptualizations are not mutually exclusive.

To our knowledge, few studies to date have used a developmental approach to investigating the structure of internalizing disorder symptoms to test whether the structure is consistent at different developmental stages. Phenotypic studies in children and adolescents provide mixed conclusions. Some support a unidimensional internalizing factor,[32-34] others identify the distress and fear dimensions,[35,36] and 1 study found that depression and anxiety disorders generally cluster into *DSM*-related categories.[37] Twin and family studies largely provide evidence for the shared etiology of mood and anxiety disorder symptoms in young people in line with the unidimensional conceptualization.[38-43] Importantly, most of these studies encompass broad age ranges spanning childhood and adolescence, thus the associations at specific developmental stages remain unknown.

Age effects are essential to consider given that depression and anxiety disorders are characterized by different ages at onset[2,5,44] and have developmentally dynamic etiologies. Environmental influences tend to decrease, while heritability increases with age and genetic innovation and attenuation take place at multiple stages.[12,13,45-50] Furthermore, depression may differ substantially pre-adolescence and postadolescence,[51-57] with 1 study finding that only the latter shares genetic influences with anxiety disorders.[40] Thus, it is plausible that despite continuing comorbidity of internalizing problems, the genetic structure changes during development.[5]

The present analyses examined these important taxonomic issues by using a genetically informed design to investigate the structure of internalizing psychopathology cross-sectionally at multiple ages: childhood, adolescence, and early adulthood. To our knowledge, this is the first study to combine 5 waves of phenotypic and genetic data on depression symptoms and 4 anxiety subscales—generalized anxiety disorder, panic, separation anxiety, and social phobia symptoms—to address this question from a developmental perspective. The genetic structures of internalizing symptoms were investigated using 3 alternative models based on previous research: *DSM-5*-related structure and unidimensional and bidimensional (fear and distress) models. Because of the mixed findings and broad age ranges of previous research, the current study tested alternative models in an exploratory manner.

Methods

Participants

The analyses used data from 2 longitudinal twin studies: waves 1 and 2 from the Emotions, Cognitions, Heredity and Outcome Study (ECHO, child twin sample) and waves 2 through 4 from the Genesis 12-19 Study (adolescent/young adult twin and sibling sample). Full recruitment details are provided elsewhere[58,59] (eAppendix in the Supplement). The studies were given ethical approval by the research ethics committees of the Institute of Psychiatry, King's College London, South London and Maudsley NHS Trust and of Goldsmiths University, London. Written informed consent was obtained from parents of children younger than 16 years and from adolescents older than 16 years. Sample characteristics are presented in **Table 1**.

Measures

Depression

Child participants completed the Children's Depression Inventory,[62] a 27-item self-report questionnaire examining affective, cognitive, and behavioral signs of current depression. Adolescents and young adults completed the Short Mood and Feelings Questionnaire,[63] a 13-item self-report measure assessing how often depressive symptoms occurred in the previous 2 weeks. Responses were summed to give total depression scores. Both measures demonstrate good reliability and validity.[62,63]

Anxiety

Children's anxiety disorder symptoms were measured using the Screen for Child Anxiety Related Emotional Disorders.[64] Children indicated how often in the last 3 months they experienced symptoms described by 41 questionnaire items. The adolescents completed the Spence Children's Anxiety Scale,[65] a 38-item self-report questionnaire tapping common anxiety symptoms. Adults completed the Revised Symptoms of Anxiety Scale,[66] an age-appropriate version of the Revised Child Anxiety and Depression Scale,[67] consisting of 36 self-report items designed to assess *DSM-IV* anxiety and depressive disorder symptoms. Responses were summed to create 4 *DSM-IV*-related anxiety subscale scores: generalized anxiety, panic/somatic symptoms, separation anxiety, and social anxiety. All measures have sound psychometric properties.[64-67]

Table 1. Sample Characteristics and Descriptive Statistics[a]

Characteristic	ECHO Study[b]		G1219 Study		
	Wave 1 Child	Wave 2 Child	Wave 2 Adolescent	Wave 3 Adolescent	Wave 4 Young Adult
Pairs, No.[c]	300	250	1372	866	896
Pairs by sex, No. (%)					
Female	169.5 (57)	141 (56)	768 (56)	520 (60)	547 (61)
Male	130.5 (43)	109 (44)	604 (44)	346 (40)	349 (39)
Age, mean (range), y/mo	8/6 (8/2-8/11)	10/1 (9/7-10/10)	15/0 (12/0-21/0)	17/0 (14/0-23/0)	20/0 (18/0-27/0)
Zygosity, No.[d]					
MZ	100	83	350	234	230
DZ	82	69	313	207	214
DZO	117	98	334	232	232
Sib	0	0	330[2]	182	201
Depression					
No.	575	499	2630	1590	1549
Mean (SD)	10.27 (6.94)	8.22 (5.82)	8.08 (6.65)	6.25 (5.33)	6.45 (5.73)
Skew	0.91	1.06	1.35	1.14	1.26
Kurtosis	3.66	4.07	4.86	3.90	4.22
α	0.81	0.82	0.86	0.79	0.90
Generalized anxiety					
No.	578	489	2632	1555	1552
Mean (SD)	5.52 (3.51)	5.08 (3.46)	5.17 (2.98)	4.87 (2.92)	4.81 (2.97)
Skew	0.42	0.67	0.87	0.81	0.82
Kurtosis	2.71	3.12	4.12	3.82	3.73
α	0.69	0.76	0.77	0.78	0.70
Panic/somatic					
No.	578	489	2619	1565	1552
Mean (SD)	7.15 (4.53)	5.71 (3.93)	2.82 (3.26)	1.40 (2.24)	3.57 (3.61)
Skew	0.57	0.86	1.83	2.55	2.13
Kurtosis	2.82	3.89	7.48	11.53	9.83
α	0.75	0.76	0.77	0.78	0.86
Separation anxiety					
No.	578	489	2622	1568	1551
Mean (SD)	7.46 (3.53)	6.06 (2.24)	2.90 (2.50)	2.72 (1.42)	2.65 (2.91)
Skew	0.11	0.42	1.35	1.02	1.83
Kurtosis	2.40	2.84	5.68	4.76	7.73
α	0.69	0.69	0.67	0.66	0.77
Social anxiety					
No.	578	489	2625	1572	1551
Mean (SD)	6.80 (2.96)	6.27 (3.03)	5.97 (3.31)	4.37 (2.70)	10.91 (5.45)
Skew	−0.12	0.05	0.52	0.54	0.43
Kurtosis	2.68	2.74	2.95	2.85	2.89
α	0.51	0.58	0.72	0.78	0.83

Abbreviations: DZO, dizygotic (opposite-sex pairs); DZ, dizygotic (same-sex pairs); ECHO, Emotions, Cognitions, Heredity and Outcome; G1219, Genesis 12-19 Study; MZ, monozygotic; sib, siblings.

[a] Different measures were used at different points, thus the means cannot be compared across certain time points. To check for measurement effects, longitudinal correlations between anxiety subscales scores are presented in eTable 4 in the Supplement. The results suggest comparable continuity of anxiety symptom scores within and across anxiety measures. The results presented on untransformed variables for comparison with other published samples.

[b] In ECHO, data from 11 twins pairs (4%) were excluded because at least 1 twin in that pair had known neurologic or receptive language impairments, autistic spectrum disorder, or attention difficulties or because researchers observed substantial difficulty completing the tasks.

[c] Total number of twin and sibling pairs in sample at each point.

[d] Twin pair zygosity was identified in both samples using a combination of parent-rated child and adolescent questionnaires[60,61] and DNA sequencing in uncertain cases. The number of twin pairs does not add up to totals owing to a number of twin pairs of unknown zygosity (ECHO wave 1 = 1; G1219 wave 2 = 45, wave 3 = 11, and wave 4 = 19). These pairs were excluded from genetic analyses.

The internal consistencies and descriptive statistics of all measures are presented in Table 1.

Analyses

Phenotypic Analyses

Descriptive statistics were conducted using Stata (StataCorp).[68] The associations between depression and anxiety subtypes were explored using full and partial correlations. For example, to investigate the unique association between depression and generalized anxiety symptoms, the scores on all other anxiety scales were controlled. This tested associations over and above the relationships with other variables that might confound the association owing to high covariance.

Genetic Analyses

The twin design compares the similarity between monozygotic (sharing 100% of their genes) and dizygotic (sharing on average 50% of their segregating genes) twin pairs. Relative differences in within-pair correlations allow estimations of the influences of additive genetics, shared environment, and non-

shared environment. Quantitative genetic methods are described comprehensively elsewhere.[69]

Models were fitted using OpenMx[70] within R,[71] a structural equation modeling package for the analysis of genetically informative data. Sampling weights were incorporated into child analyses, although they did not influence the results in a manner that would alter interpretation.[72] The weight controls for biases due to selection criteria. Lower weights were assigned to individuals from categories overrepresented in the sample and higher weights to individuals from categories underrepresented relative to the population distribution. As is standard in model fitting analysis, variables were regressed for age and sex,[73] and any with skew greater than 1 were transformed.

Univariate genetic analyses were conducted on all variables at each wave. Owing to sample size, sex differences were only examined in G1912. Scalar sex differences that examine whether males and females showed differences in variance were tested. A scalar model was fitted in twin modeling analyses for all variables except for social phobia (for which there was no difference in variance between males and females). Quantitative sex differences were tested to see whether males and females differ in magnitude of genetic and environmental influences but such differences were not found.

Three multivariate models that test different genetic structures underpinning associations between depression and anxiety subscales were fitted. They are discussed in the following order: *DSM-5*–related, unidimensional, and bidimensional (fear and distress) structures. The first model was a correlated factors solution (**Figure**, A), which is in line with the *DSM-5* conceptualization in which each disorder is classified independently but expected to correlate with other disorders. This model includes additive genetic, shared environmental, and nonshared environmental influences on each of the scales and tests whether the correlation between them is due to correlations among the genetic and environmental factors that influence each of them. Each set of influences is allowed to correlate with one another. As such, the correlation among the variables can be mediated via genetic or environmental routes.

The second model was a 1-factor independent pathway model (Figure, B). This model reflects the unidimensional conceptualization by allowing internalizing disorder symptoms to share common genetic and environmental influences. It tests whether there is a single set of common etiologic factors that influence depression and all anxiety subscales, accounting for their correlations, in addition to variable-specific factors. The model includes 1 set of common additive genetic, shared environmental, and nonshared environmental factors that influence each of the measured variables.

The third model was a 2-factor independent pathway model (Figure, C). This model is similar to the 1-factor independent pathway model but contains a second common genetic factor loading on the anxiety symptoms hypothesized to belong to the fear factor. This model reflects the bidimensional conceptualization and tests whether there are 2 common genetic factors (distress and fear) and 1 common nonshared environmental factor that influences all variables, accounting for their correlation, in addition to variable specific factors.

Models were fitted using raw data maximum likelihood. The core fit statistic was minus twice the log likelihood of the observations. This is not an overall measure of fit but provides a relative measure of fit because differences in minus twice the log likelihood between models are distributed as χ^2. Therefore, to examine the overall fit of the genetic model, we compared the minus twice the log likelihood with that of a saturated model (one which fully describes data using the maximum number of free parameters, estimating variances, covariances, and means for the raw data to get a baseline index of fit). The fit of submodels was assessed by χ^2 difference tests, the Akaike Information Criterion (AIC), and the Bayesian Information Criterion (BIC) (AIC = χ^2 - 2df; BIC = χ^2 - *k*ln[n]), with lower χ^2 values and more negative AIC and BIC values suggesting a better fit. If the difference between the AIC of 2 models was less than 10, the more parsimonious model was selected.[74] Independent pathway models are nested in the correlated factors solution, and the 1-factor independent pathway model is nested in the 2-factor independent pathway model. Information about the precision of parameter estimates was obtained by likelihood-based confidence intervals. The analyses were repeated excluding siblings to narrow the age ranges (eTable 1 in the Supplement) and including an additional anxiety subscale: fear of physical injury (only available at the 2 adolescent time points; eTable 2 in the Supplement).

Results

The results focused on the association between depression and the different anxiety subscales. The phenotypic and genetic associations among the anxiety subscales are presented elsewhere.[72,75]

Phenotypic Results

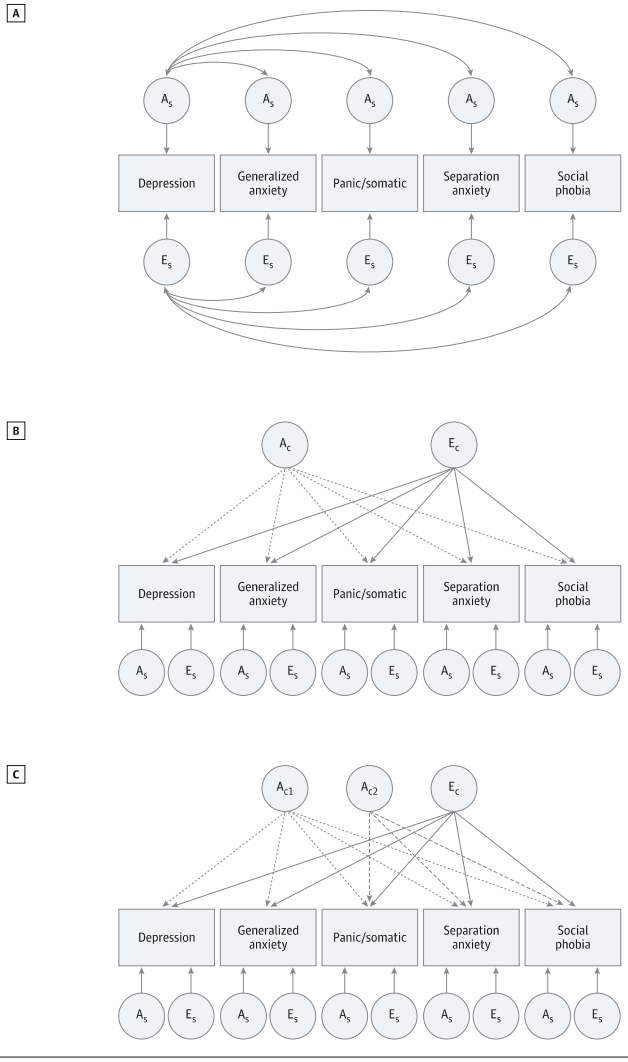
Full correlations at all ages showed that depression symptoms were significantly associated with all anxiety subscales (**Table 2**). In childhood and adolescence, depression symptoms showed significantly stronger correlations with generalized anxiety symptoms (r = 0.36 to 0.60) than with all other subscales except for panic symptoms (r = 0.28 to 0.57).

Partial correlations that controlled for all other variables within times are shown in Table 2. In childhood, when controlling for concurrent associations, depression symptoms were only significantly associated with generalized anxiety symptoms (r = 0.21 and 0.20). At 15 years, partial correlations revealed that depression symptoms were significantly associated with 3 anxiety subscales: generalized anxiety (r = 0.19), panic (r = 0.24), and social phobia (r = 0.14) symptoms. At a mean age of 17 years and in young adulthood, depression symptoms were significantly associated with all anxiety subscales even when controlling for concurrent associations.

Genetic Results

Univariate analyses revealed that genetic influences on depression and anxiety symptoms were generally small to moderate, shared environmental influences were small and non-

Figure. Multivariate Model Diagrams



The diagrams present the 3 multivariate models fitted to the data: correlated factors solution (*DSM-5* conceptualization) (A), 1-factor independent pathway model (unidimensional conceptualization) (B), and 2-factor independent pathway model (bidimensional distress and fear conceptualization) (C). The figure is for illustrative purposes only; only the genetic and nonshared environmental associations are shown. The diagram in part A illustrates only the genetic and nonshared environmental correlations between depression and anxiety subscales. A_c and A_{c1} indicate additive genetic influences acting via a common factor on all variables; A_{c2}, additive genetic influences acting via a common factor on 3 fear variables; A_s, additive genetic influences acting on a specific variable; E_c, nonshared environmental influences acting via a common factor on all variables; and E_s, nonshared environmental influences acting on a specific variable.

significant, and nonshared environmental influences were large (eTable 3 in the Supplement). Multivariate model fitting results are presented in **Table 3**. Shared environmental influences were nonsignificant and were dropped from the models without a significant deterioration of the fit in adolescence and young adulthood; fit statistics and parameter estimates are therefore presented for models with additive genetic and nonshared environmental influences.

In childhood, the most restrictive 1-factor independent pathway model was the best fitting model (**Table 4**). The common genetic factor accounted for most of the genetic influences on all anxiety subscales but did not contribute to genetic variance in depression symptoms, which instead was influenced by unique genetic influences. There were moderate to large unique nonshared environmental influences on each symptom.

Table 2. Full and Partial Correlations Between Depression and Anxiety Subscales in Childhood, Adolescence, and Early Adulthood[a]

	Childhood[b,c]		Adolescence[b,c]		Young Adulthood[b,c]
	Mean Age, y				
Correlation	8	10	15	17	20
Full correlations with depression					
Generalized anxiety	0.40 (0.33 to 0.47)	0.36 (0.31 to 0.46)	0.60 (0.58 to 0.62)	0.59 (0.56 to 0.62)	0.56 (0.53 to 0.59)
Somatic/panic	0.32 (0.25 to 0.39)	0.28 (0.20 to 0.36)	0.57 (0.54 to 0.60)	0.48 (0.44 to 0.52)	0.51 (0.47 to 0.55)
Separation anxiety	0.24 (0.16 to 0.32)	0.23 (0.15 to 0.31)	0.42 (0.39 to 0.45)	0.16 (0.11 to 0.21)	0.50 (0.46 to 0.54)
Social phobia	0.18 (0.10 to 0.26)	0.18 (0.09 to 0.26)	0.47 (0.44 to 0.50)	0.44 (0.40 to 0.48)	0.54 (0.50 to 0.57)
Partial correlations with depression[d]					
Generalized anxiety	0.21 (0.13 to .29)	0.20 (0.11 to 0.28)	0.19 (0.15 to 0.23)	0.29 (0.24 to 0.34)	0.14 (0.09 to 0.19)
Somatic/panic	0.07 (−0.01 to .15)	0.04 (−0.05 to 0.13)	0.24 (0.20 to 0.28)	0.17 (0.12 to 0.22)	0.15 (0.10 to 0.20)
Separation anxiety	−0.03 (−0.11 to 0.05)	0.04 (−0.05 to 0.13)	−0.02 (−0.06 to 0.02)	−0.14 (−0.19 to −0.09)	0.06 (0.01 to 0.11)
Social phobia	−0.05 (−0.13 to 0.03)	−0.02 (−0.11 to 0.07)	0.14 (0.10 to 0.18)	0.16 (0.11 to 0.21)	0.19 (0.14 to 0.24)

[a] Results presented on untransformed variables for comparison with other published samples. The correlations between anxiety disorder subscales are discussed elsewhere.[72,75] The additional analyses inclusive of fear of physical injury symptoms (at mean ages 15 and 17 years) are presented in eTable 2 in the Supplement.

[b] The childhood sample comes from the Emotions, Cognitions, Heredity and Outcome Study; the adolescent sample comes from waves 2 and 3 and the young adult sample comes from wave 4 of the Genesis 12-19 Study.

[c] 95% CIs are presented in parentheses; 95% CIs not inclusive of zeroes indicate significant correlations (in bold). Nonoverlapping 95% CIs mean there is a significant difference between the values. The difference in 95% CI width between the Emotions, Cognitions, Heredity and Outcome Study and Genesis 12-19 Study time points reflects the larger sample size of the Genesis 12-19 Study, which results in greater power to estimate the parameters precisely.

[d] Partial correlations controlled for all other anxiety variables within time.

In adolescence, the least restrictive model, the correlated factors solution, showed the best fit to the data in line with *DSM-5* conceptualization (**Table 5**). Genetic correlations were mostly large. Depression symptoms generally had higher genetic correlations with generalized anxiety (r = 0.71 and 0.74), panic (r = 0.78 and 0.61), and social phobia (r = 0.66 and 0.53) than with separation anxiety (r = 0.52 and 0.15) symptoms. Nonshared environmental correlations were generally moderate. Genetic influences explained a substantial proportion of the phenotypic correlation between depression and anxiety subscales (36% to 100%).

In young adulthood, a 2-factor independent pathway model showed the best fit to the data in line with a bidimensional conceptualization (**Table 6**). The first common genetic factor loaded significantly on all variables and accounted for most of the genetic variance. The second common genetic factor, specified to load on the fear variables, showed small but significant contributions to panic, separation anxiety, and social phobia symptoms. In addition, depression and generalized anxiety symptoms had significant unique genetic influences. The common nonshared environmental factor loaded significantly on all variables but there were also significant unique nonshared environmental influences on each variable.

Discussion

To our knowledge, this study is the first to investigate the phenotypic and genetic structure of internalizing disorder symptoms at 3 developmental stages. The results provide preliminary evidence for developmental differences in the associations between depression and multiple anxiety disorder symptoms, advancing the search for an evidence-based conceptualization of internalizing disorders in diagnostic manuals.

We observed different etiologic structures of internalizing disorder symptoms at 3 developmental phases, with common genetic vulnerability across depression and anxiety disorder symptoms only emerging in adolescence. Specifically, in childhood, when controlling for concurrent associations, only the generalized anxiety disorder symptoms were associated with depression. Furthermore, childhood depression was influenced by separate genetic factors from the anxiety subscales. In adolescence, comorbidity began to increase—partial correlations revealed that at 15 years of age, depression was associated with 3 anxiety disorder subscales: generalized anxiety disorder, panic, and social phobia symptoms. At this developmental stage, the etiologic structure reflected the *DSM-5* conceptualization of distinct but correlated disorders in contrast to previous studies that found support for unidimensional or bidimensional latent factor structures in young people.[32-36] These age differences may be explained by anxiety emerging in childhood, while depression peaks in adolescence,[2,36] and are in agreement with previous studies finding that depression pre-adolescence and post-adolescence may differ substantially,[51-57] which could be explained by significant new genetic influences coming online after puberty.[12,13,45,46,48]

In young adulthood, these associations broadened even further, and depression was significantly correlated with all anxiety disorder symptom scales. Genetic analyses provided support for both unidimensional[19-22] and bidimensional[26-30] conceptualizations of internalizing psychopathology. The 2 genetic factors representing distress and fear emerged, although the genetic fear factor had a relatively small influence on the fear symptoms. The current results add to a

Table 3. Multivariate Model Fit Statistics in Childhood, Adolescence, and Early Adulthood[a]

Period[b]	−2LL	*df*	Comparison With Saturated Model[c] χ^2	Δ *df*	*P* Value	Comparison With Correlated Factors Solution χ^2	Δ *df*	*P* Value	Comparison With 2-Factor Independent Pathway Model χ^2	Δ *df*	*P* Value	AIC	BIC (Size-Adjusted)
Childhood, 8 y													
Saturated model	12 970.90	2747										7476.91	13 299.68
Correlated factors solution	13 084.65	2827	113.75	80	.01							7430.65	13 211.10
2-Factor independent pathway model	13 092.67	2839	121.77	92	.02	8.02	12	.78				7414.67	13 188.77
1-Factor independent pathway model[d]	13 094.21	2842	123.31	95	.03	9.56	15	.85	1.54	3	.67	7410.21	13 182.73
Childhood, 10 y													
Saturated model	6919.34	2091										2737.34	7217.04
Correlated factors solution	7047.12	2171	127.78	80	<.01							2705.12	7161.62
2-Factor independent pathway model	7060.67	2183	141.33	92	<.01	13.55	12	.33				2694.67	7147.69
1-Factor independent pathway model[d]	7068.86	2186	149.52	95	<.01	21.74	15	.11	8.19	3	.04	2696.86	7144.15
Adolescence, 15 y													
Saturated model	34 539.26	12183										10 173.26	37 116.75
Correlated factors solution[d]	35 207.38	12664	668.12	481	<.01							9879.38	35 400.69
2-Factor independent pathway model	35 245.11	12671	705.85	488	<.01	37.73	7	<.01				9903.11	35 403.73
1-Factor independent pathway model	35 297.10	12674	757.83	491	<.01	89.72	10	<.01	51.99	3	<.01	9949.10	35 440.84
Adolescence, 17 y													
Saturated model	19 082.97	7202										4678.97	21 660.45
Correlated factors solution[d]	19 758.02	7683	675.05	481	<.01							4392.02	19 951.33
2-Factor independent pathway model	19 823.33	7690	740.36	488	<.01	65.31	7	<.01				4443.33	19 981.94
1-Factor independent pathway model	19 844.34	7693	761.37	491	<.01	86.32	10	<.01	21.01	3	<.01	4458.34	19 988.08
Young adulthood, 20 y													
Saturated model	22 999.04	7065										8869.04	25576.53
Correlated factors solution	23 556.80	7546	557.76	481	<.01							8464.80	23 750.11
2-Factor independent pathway model[d]	23 566.13	7553	567.09	488	.01	9.33	7	.23				8460.13	23 724.74
1-Factor independent pathway model	23 587.09	7556	588.05	491	.01	30.29	10	<.01	20.96	3	<.01	8475.09	23 730.83

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; −2LL, minus twice the log likelihood.

[a] Models containing additive genetic and nonshared environmental influences are presented for the adolescent and young adult samples, as shared environmental influences were not significant (eTable 3 in the Supplement) and were dropped from the multivariate models without a significant deterioration of the fit (eTable 5 in the Supplement). The analyses were repeated excluding siblings to narrow the age ranges (at mean ages 15, 17, and 20 years; eTable 1 in the Supplement) and including an additional anxiety subscale: fear of physical injury (at mean ages 15 and 17 years; eTable 2 in the Supplement). The pattern of effects and the best fitting models remained the same at each time point.

[b] The childhood sample comes from the Emotions, Cognitions, Heredity and Outcome Study; the adolescence sample comes from waves 2 and 3 and the young adult sample comes from wave 4 from the Genesis 12-19 Study. Mean ages are provided in the headers.

[c] The multivariate genetic models were significantly different from the saturated model indicating poor fit; however, this is common in studies with large sample sizes because minimal variance differences between groups can be highly statistically significant.

[d] The best fitting model was selected based on the principle of parsimony and lowest AIC and BIC value. A difference in AIC between 2 models of 2 or less provides equivalent support for both models (in which case the most parsimonious model should be chosen), a difference of 3 indicates that the lower AIC model has considerably more support, and a difference of more than 10 indicates that the lower AIC model is a substantially better fit compared with the higher AIC model.[74] At age 10 years, the difference between AIC for 1- and 2-factor independent pathway models was 2.19, thus the 1-factor independent pathway model was selected because it is more parsimonious.

debate as to whether generalized anxiety disorder ought to be classified together with depression,[14-17] and they suggest that at most ages, generalized anxiety disorder symptoms are no more closely related to depression than other anxiety subtypes. The exception is childhood, where the generalized anxiety disorder symptom subscale was the only one associated with depression, although this association was not underpinned by shared genes.

While genetic influences accounted for comorbidity, in agreement with the generalist genes hypothesis,[76] the nonshared environment was largely symptom specific across development, accounting for most of the unique variance that makes each disorder symptom a discrete condition. These results carry implications for the molecular genetic studies of depression and anxiety, which in turn may inform clinical interventions.[77-79] The results provide preliminary support for

Table 4. Model Fitting Results For 1-Factor Independent Pathway Model Results in the Child Sample[a,b]

Subscale	Common Factors			Specific Influences		
	A_c	C_c	E_c	A_s	C_s	E_s
Depression[c]						
Age 8 y	0.00 (0.00-0.19)	0.15 (0.04-0.33)	0.18 (0.09-0.30)	0.17 (0.00-0.35)	0.00 (0.00-0.22)	0.49 (0.37-0.65)
Age 10 y	0.02 (0.00-0.42)	0.15 (0.00-0.52)	0.04 (0.00-0.12)	0.00 (0.00-0.30)	0.21 (0.00-0.37)	0.58 (0.45-0.69)
Generalized anxiety						
Age 8 y	0.13 (0.01-0.30)	0.03 (0.00-0.15)	0.35 (0.22-0.49)	0.01 (0.00-0.12)	0.00 (0.00-0.07)	0.47 (0.36-0.56)
Age 10 y	0.06 (0.00-0.44)	0.14 (0.00-0.29)	0.35 (0.20-0.77)	0.01 (0.00-0.16)	0.00 (0.00-0.08)	0.43 (0.12-0.54)
Panic/somatic						
Age 8 y	0.16 (0.00-0.40)	0.07 (0.00-0.23)	0.47 (0.31-0.63)	0.04 (0.00-0.14)	0.00 (0.00-0.08)	0.25 (0.15-0.35)
Age 10 y	0.03 (0.00-0.45)	0.11 (0.00-0.31)	0.50 (0.19-0.72)	0.08 (0.00-0.24)	0.00 (0.00-0.17)	0.27 (0.11-0.54)
Separation anxiety						
Age 8 y	0.27 (0.10-0.42)	0.00 (0.00-.010)	0.26 (0.15-0.40)	0.00 (0.00-0.11)	0.00 (0.00-0.05)	0.46 (0.36-0.55)
Age 10 y	0.08 (0.00-0.55)	0.08 (0.00-0.28)	0.22 (0.03-0.34)	0.14 (0.00-0.27)	0.00 (0.00-0.14)	0.48 (0.36-0.63)
Social phobia						
Age 8 y	0.12 (0.00-0.24)	0.00 (0.00-0.08)	0.28 (0.17-0.46)	0.00 (0.00-0.07)	0.00 (0.00-0.04)	0.59 (0.49-0.68)
Age 10 y	0.38 (0.00-0.53)	0.01 (0.00-0.27)	0.21 (0.09-0.40)	0.00 (0.00-0.42)	0.00 (0.00-0.25)	0.40 (0.27-0.54)

Abbreviations: A_c, additive genetic influences acting via a common factor on all variables; A_s, additive genetic influences acting on a specific variable; C_c, shared environmental influences acting via a common factor on all variables; C_s, shared environmental influences acting on a specific variable; E_c, nonshared environmental influences acting via a common factor on all variables; E_s, nonshared environmental influences acting on a specific variable.

[a] In the child sample, shared environment was modeled and submodel comparisons revealed that shared environment could be dropped from the model without a significant deterioration of the fit. However, large sample sizes are required to reliably model effects of shared environment and we chose not to drop the shared environment parameter in the child sample to avoid artificially inflating additive genetics estimates.

[b] 95% CIs are presented in parentheses; 95% CIs not inclusive of zeroes indicate significant correlations. Nonoverlapping 95% CIs mean there is a significant difference between the values. The difference in 95% CI width between the Emotions, Cognitions, Heredity and Outcome Study and Genesis 12-19 Study time points reflects the larger sample size of the Genesis 12-19 Study, which results in greater power to estimate the parameters precisely.

[c] Depression at time 2 in the child sample (Emotions, Cognitions, Heredity and Outcome Study) showed a different pattern of parameter estimates than other variables, being influenced by moderate shared environmental factors with no genetic influence. This is due to a low power to distinguish additive genetics and shared environment in the Emotions, Cognitions, Heredity and Outcome Study sample.

Table 5. Model Fitting Results For Correlated Factor Solution Results in Adolescents[a,b,c]

Variable	Generalized Anxiety	Panic	Separation Anxiety	Social Phobia
Genetic correlations with depression				
15 y	0.71 (0.63 to 0.78)	0.78 (0.70 to 0.86)	0.52 (0.43 to 0.61)	0.66 (0.57 to 0.75)
17 y	0.74 (0.63 to 0.85)	0.61 (0.48 to 0.73)	0.15 (−0.01 to 0.32)	0.53 (0.38 to 0.66)
Nonshared environmental correlations with depression				
15 y	0.40 (0.33 to 0.47)	0.34 (0.27 to 0.41)	0.34 (0.27 to 0.42)	0.30 (0.22 to 0.38)
17 y	0.41 (0.32 to 0.50)	0.36 (0.26 to 0.45)	0.00 (−0.11 to 0.11)	0.36 (0.27 to 0.45)
Proportion of phenotypic correlation with depression due to additive genetic influences				
15 y	0.62 (0.53 to 0.71)	0.66 (0.57 to 0.74)	0.58 (0.47 to 0.69)	0.66 (0.56 to 0.76)
17 y	0.58 (0.45 to 0.69)	0.57 (0.41 to 0.71)	1.00[d]	0.50 (0.34 to 0.64)
Proportion of phenotypic correlation with depression due to nonshared environmental influences				
15 y	0.38 (0.29 to 0.47)	0.34 (0.26 to 0.43)	0.42 (0.31 to 0.53)	0.34 (0.24 to 0.44)
17 y	0.42 (0.31 to 0.55)	0.43 (0.29 to 0.58)	0.00[d]	0.50 (0.36 to 0.66)

[a] Additive genetics/nonshared environment models are presented for the adolescent sample because shared environment influences were not significant (eTable 3 in the Supplement) and were dropped from the multivariate models without a significant deterioration of the fit (eTable 5 in the Supplement). The Akaike Information Criterion values suggest that dropping shared environment led to improvement of the model fit at these 3 waves.

[b] Additional analyses inclusive of fear of physical injury symptoms (at mean ages 15 and 17) are presented in eTable 2 in the Supplement.

[c] 95% CIs are presented in parentheses; 95% CIs not inclusive of zeroes indicate significant correlations. Nonoverlapping 95% CIs mean there is a significant difference between the values. The difference in 95% CI width between the Emotions, Cognitions, Heredity and Outcome Study and Genesis 12-19 Study time points reflects larger sample size of Genesis 12-19 Study, which results in greater power to estimate the parameters precisely.

[d] 95% CIs not available due to zero environmental correlation between depression and separation anxiety symptoms at age 17 years.

Table 6. Model Fitting Results For 2-Factor Independent Pathway Model Results in Young Adults[a,b]

	Common Factors			Specific Influences	
Subscale	A_{c1}	A_{c2}	E_c	A_s	E_s
Depression	0.26 (0.17-0.35)		0.19 (0.12-0.27)	0.15 (0.08-0.22)	0.41 (0.34-0.48)
Generalized anxiety	0.33 (0.24-0.43)		0.34 (0.25-0.44)	0.07 (0.02-0.12)	0.26 (0.20-0.32)
Panic/somatic	0.26 (0.17-0.35)	0.02 (0.01-0.08)	0.29 (0.20-0.39)	0.05 (0.00-0.12)	0.37 (0.31-0.44)
Separation anxiety	0.27 (0.18-0.37)	0.04 (0.01-0.14)	0.27 (0.19-0.37)	0.05 (0.00-0.13)	0.36 (0.29-0.43)
Social phobia	0.40 (0.30-0.49)	0.07 (0.01-0.12)	0.26 (0.18-0.34)	0.00 (0.00-0.00)	0.27 (0.22-0.33)

Abbreviations: A_{c1}, additive genetic influences acting via a common factor on all variables; A_{c2}, additive genetic influences acting via a common factor on 3 fear variables; A_s, additive genetic influences acting on a specific variable; E_c, nonshared environmental influences acting via a common factor on all variables; E_s, nonshared environmental influences acting on a specific variable.

[a] Additive genetics/nonshared environment models are presented for the young adult sample because shared environment influences were not significant (eTable 3 in the Supplement) and were dropped from the multivariate models without a significant deterioration of the fit (eTable 5 in the Supplement). The Akaike Information Criterion values suggest that dropping shared environment led to improvement of the model fit at these 3 waves.

[b] 95% CIs are presented in parentheses; 95% CIs not inclusive of zeroes indicate significant correlations. Nonoverlapping 95% CIs mean there is a significant difference between the values. The difference in 95% CI width between the Emotions, Cognitions, Heredity and Outcome Study and Genesis 12-19 Study time points reflects larger sample size of Genesis 12-19 Study, which results in greater power to estimate the parameters precisely.

broadening phenotypic definitions in linkage or association studies, as including adult cases with a variety of internalizing disorders underpinned by an overarching genetic internalizing factor would lead to increasing power to detect shared susceptibility loci.[80] Conversely, the difference in the genetic results pre-adolescence and postadolescence also provides a preliminary argument for narrowing the phenotypic definitions by age.[81]

A key clinical implication of our findings was the support for transdiagnostic treatment approaches for anxiety and depression disorders, which are designed to target common elements of several disorders in 1 protocol.[82-87] The developmental pattern of the data suggests that while disorder-specific treatment may be more appropriate for pediatric patients, treatment focused on a range of symptoms common to internalizing disorders may be more appropriate for older patients. The evidence for a shared genetic etiologic factor is in agreement with the findings that internalizing disorders respond to similar interventions and therapies.[23,86-91]

The genetically informative, representative samples and multiple time points were strengths of the current study. However, a number of limitations are noteworthy. First, the child sample was smaller than the adolescent/adult sample. Although considered large for phenotypic analyses, the child sample had reduced power to examine sex differences or shared environmental influences, and parameter estimates had large confidence intervals. Replication in larger pediatric twin samples is essential. However, because of the internal replication of results across the 2 time points, interpretations seem broadly applicable for childhood. Second, the inclusion of siblings in the Genesis 12-19 Study meant there were large age ranges in adolescence and early adulthood. However, 72% of the participants were twins, and additional analyses excluding siblings suggest that the results are applicable to tighter age ranges. Third, to inform understanding of comorbidity of internalizing disorders in clinical settings, the results should be replicated in clinical samples with comorbid diagnoses and using lifetime diagnostic interviews. However, internalizing symptoms are important markers of psychopathology[92-94] and because common mental disorders are quantitative traits,[95] there is evidence that differently defined internalizing problems have the same etiology.[8,96,97] Fourth, our study included self-report measures, allowing comparisons across waves. While studies have shown that young children can accurately report on their own internalizing symptoms,[98,99] including parent-report measures at these waves may have strengthened our findings. Last, there are limitations inherent to the twin design, discussed comprehensively elsewhere.[100] These have minimal and contrasting effects on parameter estimates that should therefore be taken as indicative rather than absolute.

Conclusions

Our results suggest that the phenotypic and genetic structure of internalizing disorder symptoms may differ across development. Depression and anxiety seem to be somewhat distinct in childhood but become more associated and share most of their genetic etiology from adolescence, with an overarching internalizing genetic factor emerging in early adulthood. The results have multiple implications for further research, taxonomy, and clinical practice. They affirm the need to continue examining developmental differences in the etiology of mood and anxiety disorders to ensure that the diagnostic conceptualization of psychopathology is age appropriate.

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REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Washington, DC: American Psychiatric Association; 2013.

2. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication [published correction appears in *Arch Gen Psychiatry*. 2005;62(7):709]. *Arch Gen Psychiatry*. 2005;62(6):617-627.

3. Angold A, Costello EJ, Erkanli A. Comorbidity. *J Child Psychol Psychiatry*. 1999;40(1):57-87.

4. Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A. Prevalence and development of psychiatric disorders in childhood and adolescence. *Arch Gen Psychiatry*. 2003;60(8):837-844.

5. Beesdo K, Knappe S, Pine DS. Anxiety and anxiety disorders in children and adolescents. *Psychiatr Clin North Am*. 2009;32(3):483-524.

6. Gregory AM, Caspi A, Moffitt TE, Koenen K, Eley TC, Poulton R. Juvenile mental health histories of adults with anxiety disorders. *Am J Psychiatry*. 2007;164(2):301-308.

7. Axelson DA, Birmaher B. Relation between anxiety and depressive disorders in childhood and adolescence. *Depress Anxiety*. 2001;14(2):67-78.

8. Kendler KS, Heath AC, Martin NG, Eaves LJ. Symptoms of anxiety and symptoms of depression. *Arch Gen Psychiatry*. 1987;44(5):451-457.

9. Eley TC, Stevenson J. Using genetic analyses to clarify the distinction between depressive and anxious symptoms in children. *J Abnorm Child Psychol*. 1999;27(2):105-114.

10. Mosing MA, Gordon SD, Medland SE, et al. Genetic and environmental influences on the co-morbidity between depression, panic disorder, agoraphobia, and social phobia: a twin study. *Depress Anxiety*. 2009;26(11):1004-1011.

11. Thapar A, McGuffin P. Anxiety and depressive symptoms in childhood. *J Child Psychol Psychiatry*. 1997;38(6):651-656.

12. Zavos HM, Rijsdijk FV, Eley TC. A longitudinal, genetically informative, study of associations between anxiety sensitivity, anxiety and depression. *Behav Genet*. 2012;42(4):592-602.

13. Bergen SE, Gardner CO, Kendler KS. Age-related changes in heritability of behavioral phenotypes over adolescence and young adulthood: a meta-analysis. *Twin Res Hum Genet*. 2007;10(3):423-433.

14. Mennin DS, Heimberg RG, Fresco DM, Ritter MR. Is generalized anxiety disorder an anxiety or mood disorder? considering multiple factors as we ponder the fate of GAD. *Depress Anxiety*. 2008;25(4):289-299.

15. Hettema JM. The nosologic relationship between generalized anxiety disorder and major depression. *Depress Anxiety*. 2008;25(4):300-316.

16. Moffitt TE, Harrington H, Caspi A, et al. Depression and generalized anxiety disorder: cumulative and sequential comorbidity in a birth cohort followed prospectively to age 32 years. *Arch Gen Psychiatry*. 2007;64(6):651-660.

17. Goldberg D. Towards *DSM-V*: the relationship between generalized anxiety disorder and major depressive episode. *Psychol Med*. 2008;38(11):1671-1675.

18. Beesdo K, Pine DS, Lieb R, Wittchen HU. Incidence and risk patterns of anxiety and depressive disorders and categorization of generalized anxiety disorder. *Arch Gen Psychiatry*. 2010;67(1):47-57.

19. Fergusson DM, Horwood LJ, Boden JM. Structure of internalising symptoms in early adulthood. *Br J Psychiatry*. 2006;189(6):540-546.

20. Seeley JR, Kosty DB, Farmer RF, Lewinsohn PM. The modeling of internalizing disorders on the basis of patterns of lifetime comorbidity. *J Abnorm Psychol*. 2011;120(2):308-321.

21. Krueger RF, Caspi A, Moffitt TE, Silva PA. The structure and stability of common mental disorders (*DSM-III-R*): a longitudinal-epidemiological study. *J Abnorm Psychol*. 1998;107(2):216-227.

22. Eaton NR, Krueger RF, Oltmanns TF. Aging and the structure and long-term stability of the internalizing spectrum of personality and psychopathology. *Psychol Aging*. 2011;26(4):987-993.

23. Goldberg DP, Krueger RF, Andrews G, Hobbs MJ. Emotional disorders: cluster 4 of the proposed meta-structure for *DSM-V* and *ICD-11*. *Psychol Med*. 2009;39(12):2043-2059.

24. Kendler KS, Aggen SH, Knudsen GP, Røysamb E, Neale MC, Reichborn-Kjennerud T. The structure of genetic and environmental risk factors for syndromal and subsyndromal common *DSM-IV* axis I and all axis II disorders. *Am J Psychiatry*. 2011;168(1):29-39.

25. Goes FS, McCusker MG, Bienvenu OJ, et al; National Institute of Mental Health Genetics Initiative Bipolar Disorder Consortium. Co-morbid anxiety disorders in bipolar disorder and major depression: familial aggregation and clinical characteristics of co-morbid panic disorder, social phobia, specific phobia and obsessive-compulsive disorder. *Psychol Med*. 2012;42(7):1449-1459.

26. Sellbom M, Ben-Porath YS, Bagby RM. On the hierarchical structure of mood and anxiety disorders: confirmatory evidence and elaboration of a model of temperament markers. *J Abnorm Psychol*. 2008;117(3):576-590.

27. Watson D. Rethinking the mood and anxiety disorders: a quantitative hierarchical model for DSM-V. *J Abnorm Psychol*. 2005;114(4):522-536.

28. Eaton NR, Krueger RF, Markon KE, et al. The structure and predictive validity of the internalizing disorders. *J Abnorm Psychol*. 2013;122(1):86-92.

29. Vollebergh WA, Iedema J, Bijl RV, de Graaf R, Smit F, Ormel J. The structure and stability of common mental disorders: the NEMESIS Study. *Arch Gen Psychiatry*. 2001;58(6):597-603.

30. Slade T, Watson D. The structure of common *DSM-IV* and *ICD-10* mental disorders in the Australian general population. *Psychol Med*. 2006;36(11):1593-1600.

31. Kendler KS, Prescott CA, Myers J, Neale MC. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Arch Gen Psychiatry*. 2003;60(9):929-937.

32. Gomez R, Vance A, Gomez RM. The factor structure of anxiety and depressive disorders in a sample of clinic-referred adolescents. *J Abnorm Child Psychol*. 2014;42(2):321-332.

33. Trosper SE, Whitton SW, Brown TA, Pincus DB. Understanding the latent structure of the emotional disorders in children and adolescents. *J Abnorm Child Psychol*. 2012;40(4):621-632.

34. Krueger RF, Finger MS. Using item response theory to understand comorbidity among anxiety and unipolar mood disorders. *Psychol Assess*. 2001;13(1):140-151.

35. Lahey BB, Rathouz PJ, Van Hulle C, et al. Testing structural models of *DSM-IV* symptoms of common forms of child and adolescent psychopathology. *J Abnorm Child Psychol*. 2008;36(2):187-206.

36. Lahey BB, Applegate B, Waldman ID, Loft JD, Hankin BL, Rick J. The structure of child and adolescent psychopathology. *J Abnorm Psychol*. 2004;113(3):358-385.

37. Higa-McMillan CK, Smith RL, Chorpita BF, Hayashi K. Common and unique factors associated with *DSM-IV-TR* internalizing disorders in children. *J Abnorm Child Psychol*. 2008;36(8):1279-1288.

38. Lahey BB, Van Hulle CA, Singh AL, Waldman ID, Rathouz PJ. Higher-order genetic and environmental structure of prevalent forms of child and adolescent psychopathology. *Arch Gen Psychiatry*. 2011;68(2):181-189.

39. Cosgrove VE, Rhee SH, Gelhorn HL, et al. Structure and etiology of co-occurring internalizing and externalizing disorders in adolescents. *J Abnorm Child Psychol*. 2011;39(1):109-123.

40. Silberg JL, Rutter M, Eaves L. Genetic and environmental influences on the temporal association between earlier anxiety and later depression in girls [erratum appears in *Biol Psychiatry*. 2001;50(5):393]. *Biol Psychiatry*. 2001; 49(12):1040-1049.

41. Lieb R, Isensee B, Höfler M, Pfister H, Wittchen H-U. Parental major depression and the risk of depression and other mental disorders in offspring: a prospective-longitudinal community study. *Arch Gen Psychiatry*. 2002;59(4):365-374.

42. Hudson JI, Mangweth B, Pope HG Jr, et al. Family study of affective spectrum disorder. *Arch Gen Psychiatry*. 2003;60(2):170-177.

43. Starr L, Conway C, Hammen C, Brennan P. Transdiagnostic and disorder-specific models of intergenerational transmission of internalizing pathology. *Psychol Med*. 2014;44(1):161-172.

44. Wittchen HU, Kessler RC, Pfister H, Lieb M. Why do people with anxiety disorders become depressed? a prospective-longitudinal community study. *Acta Psychiatr Scand Suppl*. 2000;102(406): 14-23.

45. Kendler KS, Gardner CO, Lichtenstein P. A developmental twin study of symptoms of anxiety and depression. *Psychol Med*. 2008;38(11):1567-1575.

46. Scourfield J, Rice F, Thapar A, Harold GT, Martin N, McGuffin P. Depressive symptoms in children and adolescents. *J Child Psychol Psychiatry*. 2003;44(7):968-976.

47. Rice F, Harold GT, Thapar A. Assessing the effects of age, sex and shared environment on the genetic aetiology of depression in childhood and adolescence. *J Child Psychol Psychiatry*. 2002;43 (8):1039-1051.

48. Kendler KS, Gardner CO, Annas P, Neale MC, Eaves LJ, Lichtenstein P. A longitudinal twin study of fears from middle childhood to early adulthood: evidence for a developmentally dynamic genome. *Arch Gen Psychiatry*. 2008;65(4):421-429.

49. Franić S, Middeldorp CM, Dolan CV, Ligthart L, Boomsma DI. Childhood and adolescent anxiety and depression: beyond heritability. *J Am Acad Child Adolesc Psychiatry*. 2010;49(8):820-829.

50. Lau JYF, Eley TC. Changes in genetic and environmental influences on depressive symptoms across adolescence and young adulthood. *Br J Psychiatry*. 2006;189:422-427.

51. Rutter M, Kim-Cohen J, Maughan B. Continuities and discontinuities in psychopathology between childhood and adult life. *J Child Psychol Psychiatry*. 2006;47(3-4):276-295.

52. Harrington R, Fudge H, Rutter M, Pickles A, Hill J. Adult outcomes of childhood and adolescent depression, I: psychiatric status. *Arch Gen Psychiatry*. 1990;47(5):465-473.

53. Weissman MM, Wolk S, Wickramaratne P, et al. Children with prepubertal-onset major depressive disorder and anxiety grown up. *Arch Gen Psychiatry*. 1999;56(9):794-801.

54. Harrington R, Rutter M, Fombonne E. Developmental pathways in depression. *Dev Psychopathol*. 1996;8:601-616.

55. Kaufman J, Martin A, King RA, Charney D. Are child-, adolescent-, and adult-onset depression one and the same disorder? *Biol Psychiatry*. 2001;49 (12):980-1001.

56. Jaffee SR, Moffitt TE, Caspi A, Fombonne E, Poulton R, Martin J. Differences in early childhood risk factors for juvenile-onset and adult-onset depression. *Arch Gen Psychiatry*. 2002;59(3): 215-222.

57. Rice F, Harold G, Thapar A. The genetic aetiology of childhood depression: a review. *J Child Psychol Psychiatry*. 2002;43(1):65-79.

58. Eley TC, Gregory AM, Clark DM, Ehlers A. Feeling anxious: a twin study of panic/somatic ratings, anxiety sensitivity and heartbeat perception in children. *J Child Psychol Psychiatry*. 2007;48(12):1184-1191.

59. McAdams TA, Gregory AM, Rowe R, et al. The Genesis 12-19 (G1219) Study: a twin and sibling study of gene-environment interplay and adolescent development in the UK. *Twin Res Hum Genet*. 2013;16(1):134-143.

60. Price TS, Freeman B, Craig I, Petrill SA, Ebersole L, Plomin R. Infant zygosity can be assigned by parental report questionnaire data. *Twin Res*. 2000;3(3):129-133.

61. Cohen DJ, Dibble E, Grawe JM, Pollin W. Reliably separating identical from fraternal twins. *Arch Gen Psychiatry*. 1975;32(11):1371-1375.

62. Kovacs M. The Children's Depression, Inventory (CDI). *Psychopharmacol Bull*. 1985;21(4): 995-998.

63. Angold A, Costello EJ, Messer SC, Pickles A, Winder F, Silver D. The development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. *Int J Method Psych*. 1995;5:1-12.

64. Birmaher B, Brent DA, Chiappetta L, Bridge J, Monga S, Baugher M. Psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED): a replication study. *J Am Acad Child Adolesc Psychiatry*. 1999;38(10):1230-1236.

65. Spence SH. A measure of anxiety symptoms among children. *Behav Res Ther*. 1998;36(5): 545-566.

66. Gregory AM, Buysse DJ, Willis TA, et al. Associations between sleep quality and anxiety and depression symptoms in a sample of young adult twins and siblings. *J Psychosom Res*. 2011;71(4): 250-255.

67. Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE. Assessment of symptoms of *DSM-IV* anxiety and depression in children. *Behav Res Ther*. 2000;38(8):835-855.

68. StataCorp. *Stata Statistical Software: Release 10*. College Station, TX: StataCorp LP; 2007.

69. Rijsdijk FV, Sham PC. Analytic approaches to twin data using structural equation models. *Brief Bioinform*. 2002;3(2):119-133.

70. Boker S, Neale M, Maes H, et al. OpenMx: an open source extended structural equation modeling framework. *Psychometrika*. 2011;76(2): 306-317.

71. TeamRDC. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2010.

72. Lau JYF, Gregory AM, Goldwin MA, Pine DS, Eley TC. Assessing gene-environment interactions on anxiety symptom subtypes across childhood and adolescence. *Dev Psychopathol*. 2007;19(4): 1129-1146.

73. McGue M, Bouchard TJ Jr. Adjustment of twin data for the effects of age and sex. *Behav Genet*. 1984;14(4):325-343.

74. Wagenmakers E-J, Farrell S. AIC model selection using Akaike weights. *Psychon Bull Rev*. 2004;11(1): 192-196.

75. Waszczuk MA, Zavos HM, Eley TC. Genetic and environmental influences on relationship between anxiety sensitivity and anxiety subscales in children. *J Anxiety Disord*. 2013;27(5):475-484.

76. Eley TC. General genes: A new theme in developmental psychopathology. *Curr Dir Psychol*. 1997;6:90-95.

77. Lester KJ, Eley TC. Therapygenetics: using genetic markers to predict response to psychological treatment for mood and anxiety disorders. *Biol Mood Anxiety Disord*. 2013;3(1):4.

78. Eley TC, Hudson JL, Creswell C, et al. Therapygenetics: the 5HTTLPR and response to psychological therapy. *Mol Psychiatry*. 2012;17(3): 236-237.

79. Keers R, Aitchison KJ. Pharmacogenetics of antidepressant response. *Expert Rev Neurother*. 2011;11(1):101-125.

80. O'Reilly PF, Hoggart CJ, Pomyen Y, et al. MultiPhen: joint model of multiple phenotypes can increase discovery in GWAS. *PLoS One*. 2012;7(5): e34861.

81. Zaitlen N, Lindström S, Pasaniuc B, et al. Informed conditioning on clinical covariates increases power in case-control association studies. *PLoS Genet*. 2012;8(11):e1003032.

82. Barlow DH, Allen LB, Choate ML. Toward a unified treatment for emotional disorders. *Behav Ther*. 2004;35(2):205-230. doi:10.1016/S0005-7894(04)80036-4.

83. Craske MG, Rose RD, Lang A, et al. Computer-assisted delivery of cognitive behavioral therapy for anxiety disorders in primary-care settings. *Depress Anxiety*. 2009;26(3):235-242.

84. Wilamowska ZA, Thompson-Hollands J, Fairholme CP, Ellard KK, Farchione TJ, Barlow DH. Conceptual background, development, and preliminary data from the unified protocol for transdiagnostic treatment of emotional disorders. *Depress Anxiety*. 2010;27(10):882-890.

85. Titov N, Dear BF, Schwencke G, et al. Transdiagnostic internet treatment for anxiety and depression: a randomised controlled trial. *Behav Res Ther*. 2011;49(8):441-452.

86. McEvoy PM, Nathan P, Norton PJ. Efficacy of transdiagnostic treatments: a review of published outcome studies and future research directions. *J Cogn Psychother*. 2009;23(1):20-33.

87. Clark DA, Taylor S. The transdiagnostic perspective on cognitive-behavioral therapy for anxiety and depression: new wine for old wineskins? *J Cogn Psychother*. 2009;23(1):60-66.

88. Brown TA, Antony MM, Barlow DH. Diagnostic comorbidity in panic disorder. *J Consult Clin Psychol*. 1995;63(3):408-418.

89. Kendall PC, Brady EU, Verduin TL. Comorbidity in childhood anxiety disorders and treatment outcome. *J Am Acad Child Adolesc Psychiatry*. 2001; 40(7):787-794.

90. Furukawa TA, Watanabe N, Omori IM. What (no) differences in responses to three classes of psychotropics can teach us about distinctions between generalized anxiety disorder and major depressive disorder. In: Goldberg DP, Kendler KS, Sirovatka P, Regier DA, eds. *Diagnostic Issues in Depression and Generalized Anxiety Disorder: Refining the Research Agenda for DSM-V.* Washington, DC: American Psychiatric Association; 2010.

91. Morilak DA, Frazer A. Antidepressants and brain monoaminergic systems: a dimensional approach to understanding their behavioural effects in depression and anxiety disorders. *Int J Neuropsychopharmacol*. 2004;7(2):193-218.

92. Balázs J, Miklósi M, Keresztény A, et al. Adolescent subthreshold-depression and anxiety: psychopathology, functional impairment and increased suicide risk. *J Child Psychol Psychiatry*. 2013;54(6):670-677.

93. Fergusson DM, Horwood LJ, Ridder EM, Beautrais AL. Subthreshold depression in adolescence and mental health outcomes in adulthood. *Arch Gen Psychiatry*. 2005;62(1):66-72.

94. Pickles A, Rowe R, Simonoff E, Foley D, Rutter M, Silberg J. Child psychiatric symptoms and psychosocial impairment. *Br J Psychiatry*. 2001;179:230-235.

95. Plomin R, Haworth CM, Davis OS. Common disorders are quantitative traits. *Nat Rev Genet*. 2009;10(12):872-878.

96. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. Major depression and generalized anxiety disorder. *Arch Gen Psychiatry*. 1992;49(9):716-722.

97. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. A population-based twin study of major depression in women: the impact of varying definitions of illness. *Arch Gen Psychiatry*. 1992;49(4):257-266.

98. Merrell KW, McClun LA, Kempf KKG, Lund J. Using self-report assessment to identify children with internalizing problems: validity of the internalizing symptoms scale for children. *J Psychoed Assess*. 2002;20:223-239.

99. Michael KD, Merrell KW. Reliability of children's self-reported internalizing symptoms over short to medium-length time intervals. *J Am Acad Child Adolesc Psychiatry*. 1998;37(2):194-201.

100. Plomin R, DeFries JC, McClearn GE, McGuffin P. *Behavioral genetics.* New York, NY: Worth Publishers; 2008.

4. CHAPTER 4 - THE CONTINUITY AND CHANGE OF AETIOLOGICAL INFLUENCES ON DEPRESSION, ANXIETY SYMPTOMS AND THEIR CO-OCCURRENCE ACROSS ADOLESCENCE AND YOUNG ADULTHOOD.

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Supplementary materials for this chapter are presented in **Appendix B**

4.1. ABSTRACT

Background: Depression and anxiety persist within and across diagnostic boundaries. The manner in which common versus disorder-specific genetic and environmental influences operate across development to maintain internalizing disorders and their comorbidity is unclear. The current study investigated the stability and change of etiological influences on depression, panic, generalized, separation and social anxiety symptoms, and their co-occurrence, across adolescence and young adulthood.

Methods: 2,619 twins/siblings prospectively reported symptoms of depression and anxiety at mean ages 15, 17 and 20 years.

Results: Each symptom scale showed a similar pattern of moderate continuity across development, largely underpinned by genetic stability. New genetic influences contributing to change in the developmental course of the symptoms emerged at each time point. All symptom scales correlated moderately with one another over time. Genetic influences, both stable and time-specific, overlapped considerably between the scales. Non-shared environmental influences were largely time- and symptom-specific, but some contributed moderately to the stability of depression and anxiety symptom scales. These stable, longitudinal environmental influences were highly correlated between the symptoms.

Conclusions: The results highlight both stable and dynamic etiology of depression and anxiety symptom scales. They provide preliminary evidence that stable as well as newly emerging genes contribute to the comorbidity between depression and anxiety across adolescence and young adulthood. Conversely, environmental influences are largely time-specific and contribute to change in symptoms over time. The results inform molecular genetics research and transdiagnostic treatment and prevention approaches.

4.2. INTRODUCTION

Depression and anxiety disorders commonly co-occur (Angold, Costello, & Erkanli, 1999; Beesdo, Knappe, & Pine, 2009; Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Gregory et al., 2007; Kessler, Chiu, Demler, Merikangas, & Walters, 2005) and share multiple risk factors (Axelson & Birmaher, 2001), including substantial genetic overlap (Eley & Stevenson, 1999; Kendler, Heath, Martin, & Eaves, 1987; Mosing et al., 2009; Thapar & McGuffin, 1997; Waszczuk, Zavos, Gregory, & Eley, 2014; Zavos, Rijsdijk, & Eley, 2012). Both are chronic and show *homotypic* (within-disorder) and *heterotypic* (across-disorder) continuity over time (Costello et al., 2003; Ferdinand, Dieleman, Ormel, & Verhulst, 2007; Goodwin, Fergusson, & Horwood, 2004; Gregory et al., 2007; Lahey, Zald, Hakes, Krueger, & Rathouz, 2014; Merikangas, 1993; Moffitt et al., 2007; Pine, Cohen, & Brook, 2001; Rutter, Kim-Cohen, & Maughan, 2006; Trzaskowski, Zavos, Haworth, Plomin, & Eley, 2011). Homotypic continuity suggests a degree of specificity of the constructs, in line with DSM-5 categorization (American Psychiatric Association, 2013), in that the construct shows a fairly stable presentation. Additionally, heterotypic continuity also indicates an overlap between them, as proposed by transdiagnostic theories (Insel et al., 2010; Wilamowska et al., 2010). Furthermore, there are developmental differences in the phenotypic and genetic relationship between depression and *different* anxiety disorders (Axelson & Birmaher, 2001; Beesdo et al., 2009; Beesdo, Pine, Lieb, & Wittchen, 2010; Bergen, Gardner, & Kendler, 2007; Goldberg, 2008; Hettema, 2008; Mennin, Heimberg, Fresco, & Ritter, 2008; Moffitt et al., 2007; Waszczuk et al., 2014). For example, we recently found age differences in phenotypic and genetic overlap between depression and a range of anxiety symptoms, with the association between these symptoms increasing markedly from adolescence, indicating developmentally dynamic etiology of internalizing problems (Waszczuk et al., 2014). As a result, genetic and environmental influences are likely to vary in their contribution to the continuity of depression, different anxiety subtypes, and their longitudinal co-occurrence across time. Understanding how these risk and maintenance factors operate across development is crucial for informing successful prevention and

intervention strategies. Thus, the current study investigated the continuity and change of genetic and environmental influences on homotypic and heterotypic continuity of depression and four anxiety symptom clusters across adolescence and young adulthood.

Homotypic Continuity

To date longitudinal twin studies have focused largely on the contribution of genetic and environmental influences to homotypic continuity of depression, anxiety, or composite internalizing symptoms. Some studies have found that stable genetic influences contribute substantially to homotypic continuity across the life span (Garcia et al., 2013; Gillespie et al., 2004; O'Connor, Neiderhiser, Reiss, Hetherington, & Plomin, 1998; Trzaskowski et al., 2011; Waszczuk, Zavos, & Eley, 2013). Conversely, other studies, primarily those of children and adolescents, have found that alongside genetic stability, new genetic influences emerge that contribute to change in symptoms over time (Bartels et al., 2004; Haberstick, Schmitz, Young, & Hewitt, 2005; Kendler, Gardner, Annas, et al., 2008; Kendler, Gardner, & Lichtenstein, 2008; Lau & Eley, 2006; Lewis & Plomin, 2015; Nivard et al., 2014; Scourfield et al., 2003; van der Valk, van den Oord, Verhulst, & Boomsma, 2003; Zavos et al., 2012). This is in line with evidence that childhood and adolescence are more genetically dynamic than adulthood (Nivard et al., 2014).

The role of shared environmental influences is also unclear. Evidence from child samples suggests that stable shared environmental influences contribute to the homotypic continuity of symptoms (Bartels et al., 2004; Kendler, Gardner, Annas, et al., 2008; Schmitz, Fulker, & Mrazek, 1995; Scourfield et al., 2003; Silberg, Rutter, & Eaves, 2001; van der Valk et al., 2003), as well as to heterotypic continuity between different anxiety traits across time (Trzaskowski et al., 2011). This has generally not been replicated in older twins, possibly because shared environmental influences play a diminishing role in adolescence and adulthood (Rapee, Schniering, & Hudson, 2009). Finally, non-shared environmental influences tend to be time-specific and contribute to change rather than stability of internalizing symptoms over time

(Bartels et al., 2004; Garcia et al., 2013; Haberstick et al., 2005; Lau & Eley, 2006; Lewis & Plomin, 2015; Scourfield et al., 2003; van der Valk et al., 2003; Zavos et al., 2012). However, some studies have found that non-shared environmental influences can contribute to the homotypic continuity of depression and anxiety symptoms (Kendler et al., 2011; Kendler, Gardner, Annas, et al., 2008; Nivard et al., 2014; O'Connor et al., 1998).

Despite remarkable heterogeneity of anxiety disorders, to our knowledge only two studies to date have investigated the etiology of homotypic continuity of different anxiety symptom clusters. The first study examined three types of phobia from childhood to adulthood, and found more stable shared environmental influences on animal than situational and blood/injury fears (Kendler, Gardner, Annas, et al., 2008). The second study investigated genetic and environmental influences on panic, separation and generalized anxiety symptoms across middle childhood, and found genetic stability and largely time-specific environmental influences consistently in the three symptoms (Waszczuk et al., 2013). To address this gap in the literature, the first aim of the current study was to systematically explore and compare the genetic and environmental influences on the homotypic continuity of depression and four anxiety symptom clusters – panic, generalized, separation and social anxiety. We focused specifically on adolescence and young adulthood, developmental periods characterized by increased prevalence of depression and some of the anxiety disorders (Costello et al., 2003), and a time of substantial maturation of emotional processing (Blakemore, 2008; Kadosh, Linden, & Lau, 2013; Yurgelun-Todd, 2007). In line with certain previous studies in adolescents we hypothesized that: (i) stable genetic factors would substantially contribute to homotypic continuity of each symptom in this age group, (ii) there would be time-specific genetic and environmental influences that contribute to change in the course of each symptom. We also explored whether there would be differences in the etiology of homotypic continuity across time between the symptom scales.

Heterotypic continuity

To date only two studies have examined how dynamic changes in etiological influences contribute to the comorbidity of internalizing disorders over time. The first study found that common genetic influences on childhood overanxious disorder and phobias continue to adolescence, where they also predict variance in adolescent depression (Silberg et al., 2001). Furthermore, shared environmental influences contributed to heterotypic continuity between some of the internalizing symptoms. The second study found that the genetic influences on childhood separation anxiety disorder continue to influence adult onset panic attacks (Roberson-Nay, Eaves, Hettema, Kendler, & Silberg, 2012). However, the degree to which stable and time-specific etiological influences are shared between depression and anxiety disorder symptoms across development remains largely unknown. Understanding how genetic and environmental influences contribute to the comorbidity of internalizing symptoms over time might provide clinically-relevant insights in the context of growing interest in transdiagnostic interventions. Given a remarkably high genetic overlap and small to moderate non-shared environmental correlations between these multiple disorders (Eley & Stevenson, 1999; Kendler et al., 1987; Mosing et al., 2009; Spatola et al., 2007; Thapar & McGuffin, 1997; Waszczuk et al., 2014; Zavos et al., 2012), we tentatively hypothesized that: (iii) both stable and time-specific genetic influences would contribute to the longitudinal comorbidity between depression and anxiety symptom scales, (iv) environmental influences would not contribute markedly to the longitudinal comorbidity.

4.3. METHODS

4.3.1. PARTICIPANTS

The analyses use data from waves 2-4 (hereon referred to as times 1-3 respectively) of a longitudinal twin and sibling study, the Genesis 1219 (G1219). Full details are provided elsewhere (McAdams et al., 2013). The study was given ethical approval by the Research Ethics

Committee of the Institute of Psychiatry, Kings College, London, South London and Maudsley NHS Trust and Goldsmiths, University of London. Informed consent was obtained from parents of adolescents under 16 years and from participants over 16. The sample size at time 1 was 1,372 pairs (350 monozygotic (MZ), 313 dizygotic same-sex (DZss), 334 dizygotic opposite-sex (DZos), 330 siblings; 56% female; mean age 15 years (range 12-21, SD=1.67)), at time 2 it was 866 pairs (234 MZ, 207 DZss, 232 DZos, 182 siblings; 60% female; mean age 17 years (range 14-23, SD=1.67)), and at time 3 it was 896 pairs (230 MZ, 214 DZss, 232 DZos, 201 siblings; 61% female; mean age 20 years (range 18-27, SD=1.76)). The inclusion of siblings inevitably resulted in large age ranges; however 72% of the participants were twins with a tighter age range (e.g. at time 2, age SD=1.11, range=15-19 for twins, age SD=1.97, range=15-23 for siblings). Attrition was predicted by SES (responses were more likely from individuals with parents reporting higher qualifications and home ownership), delinquency (individuals reporting lower levels of delinquent behaviour were more likely to stay in the study) and sex (females were more likely than males to remain in the study), but not by zygosity and internalizing symptoms.

4.3.2. MEASURES

Depression symptoms

At each time the participants completed the Short Mood and Feelings Questionnaire (Angold et al., 1995), a 13-item self-report measure assessing how often depression symptoms occurred in the past two weeks. Responses were summed to give total depression scores. The measure demonstrates good reliability and validity (Angold et al., 1995) and the internal consistency was very high in the current study (α=.79-.90).

Anxiety symptoms

The adolescents (times 1 and 2) completed the Spence Children's Anxiety Scale (Spence, 1998); a 38-item self-report questionnaire tapping common anxiety symptoms. Adults (time 3) completed the Revised Symptoms of Anxiety Scale (Gregory et al., 2011), an age-appropriate version of the Revised Child Anxiety and Depression Scale (Chorpita, Yim, Moffitt, Umemoto, &

Francis, 2000), consisting of 36 self-report items designed to assess DSM-IV anxiety disorder symptoms. Responses were summed to create four DSM-IV-related anxiety symptom scales: panic, generalized, separation and social anxiety. Subscales were originally derived using exploratory factor analyses conducted in large, independent samples (Chorpita et al., 2000; Spence, 1997, 1998). All measures have good internal consistency (α=.66-.77 for separation anxiety, α=.70-.90 for all other scales) (Birmaher et al., 1999; Chorpita et al., 2000; Gregory et al., 2011; Spence, 1998).

The internal consistencies and descriptive statistics of all measures were comparable to published samples and are presented elsewhere (Waszczuk et al., 2014).

4.3.3. ANALYSES

The twin design compares the similarity between MZ (sharing 100% of their genes) and DZ (sharing on average 50% of their segregating genes) twin pairs. Differences in within-pair correlations allows estimations of the influences of additive genetics (A), shared environment (C), factors that contribute to phenotypic similarity between siblings) and non-shared environment (E, factors that contribute to phenotypic differences between siblings). Quantitative genetic methods are described comprehensively elsewhere (Plomin, DeFries, Knopik, & Neiderhiser, 2013; Rijsdijk & Sham, 2002).

Models were fitted using OpenMx (Boker et al., 2011) within R (www.R-project.org (TeamRDC, 2010)), a structural equation modeling package for genetically informative data. As is standard in model fitting analysis, variables were regressed for age and sex(McGue & Bouchard, 1984), and any with skew greater than 1 were transformed.

Models were fitted using raw data maximum likelihood. The core fit statistic was minus twice the log likelihood (-2LL) of the observations. This is not an overall measure of fit, but provides a relative measure of fit, since differences in -2LL between models are distributed as χ^2. To examine the overall fit of the genetic model we compared the -2LL to that of a saturated

model (which fully describes data using the maximum number of free parameters, estimating variances, covariances and means for the raw data to get a baseline index of fit). The fit of sub-models was assessed by χ^2 difference tests, the Akaike's and the Bayesian's Information Criterion, with lower values suggesting a better fit. If the difference between the AIC of two models was less than 10, the more parsimonious model was selected (Wagenmakers & Farrell, 2004). Information about the precision of parameter estimates was obtained by likelihood-based confidence intervals.

Univariate genetic analyses were conducted on all variables at each time. Males and females showed differences in variance on all variables except for social anxiety, and a scalar was fitted to account for this difference (Waszczuk et al., 2014). Quantitative sex differences were tested to see whether males and females differ in magnitude of genetic and environmental influences, but such differences were not found. Finally, comparisons indicated that covariances, means and variances could be equated across DZ twins and siblings for all variables.

Homotypic continuity

Multivariate models best suited to investigate specific research questions were chosen a priori. The Cholesky decomposition (Figure 4.1a) was used to examine the *homotypic continuity* of etiological influences separately for each variable. The Cholesky decomposition assumes three distinct sets of genetic and environmental influences on a variable at each time point. A1 and E1 are common factors on the first variable (paths $a1_1$ and $e1_1$) that can also influence the remaining two variables (paths $a1_{2\text{-}3}$ and $e1_{2\text{-}3}$, reflecting continuity from time 1 to times 2 and 3). A2 and E2 influence the second variable (paths $a2_2$ and $e2_2$, reflecting new genes emerging at time 2) and can also influence the third variable over and above the influences accounted for by A1 and E1 (paths $a2_3$ and $e2_3$, reflecting continuity from time 2 to time 3). A3 and E3 are unique influences specific to the third variable only (paths $a3_3$ and $e3_3$, reflecting new influences emerging at time 3). Total A and E effects on each individual measure can be

obtained by summing all squared paths to that measure (e.g. the proportion of total variance in third variable explained by A influences is obtained by summing squared paths $a1_3$, $a2_3$ and $a3_3$).

Heterotypic continuity

The common pathway model (Figure 4.1b*)* was fitted in order to investigate the stability and change of the etiological influences shared between depression and anxiety symptom scales across development, to inform the mechanisms underpinning *heterotypic continuity* across time. The model is illustrated on Figure 4.1b (with just three variables for clarity); the model was run with all five variables included, each measured at three time points. This model assumes five latent factors; each underlying a variable assessed three times. For example, the depression latent factor captures the stability of the depression symptoms across times 1-3. Variance of each latent factor is then decomposed into genetic (A_l) and environmental (E_l) influences to assess the etiological factors underpinning the stability of each symptom. Of note, E_l is free from time-specific measurement error but not from shared measurement error. The genetic and environmental correlations between the latent factors (r_{Al} and r_{El}) represent the degree of developmental stability common to depression and anxiety symptom scales. Any remaining variance (not explained by the latent factor) is then calculated as variable-specific genetic and environmental influences (A_s and E_s). The variable-specific etiological influences include genetic and environmental influences that emerge at later time points, and are allowed to correlate with the within-time influences on all other variables (r_{As} and r_{Es}), capturing time-specific associations between them.

4.4. RESULTS

Phenotypic correlations

The longitudinal correlations between the variables across the three time points are presented in Table 4.1. All variables showed moderate homotypic continuity (r=.35-.58). The heterotypic

correlations between the different anxiety symptom clusters, and between depression and each of the anxiety scales, were similar in magnitude and generally moderate (r=.12-.46 and r=.11-.39, respectively). Homotypic correlations were generally larger than heterotypic correlations, but tended to decrease at longer time intervals (time 1 to time 3).

Homotypic continuity

The Cholesky decompositions show the effect of stable and new genetic and environmental factors across the three times, separately for each of the five symptom scales. The results were similar for depression and each anxiety symptom scale (Figure 4.2*)*. First, there was evidence of substantial genetic continuity, whereby genetic factors influencing symptoms at any one age continue to affect the symptom at subsequent ages. Second, the early influences gradually declined over time. For example, the first set of genetic factors (corresponding to path $a1_1$ on Figure 4.1a) accounted for 45% of the variance in generalized anxiety symptoms at age 15, but reduced to 21% by age 17 (path $a1_2$) and 18% by age 20 (path $a1_3$). Third, new genetic factors emerged at each age (paths $a2_2$ and $a3_3$). Genetic influences that emerged at age 17 continued to influence symptoms at age 20 (path $a2_3$) in generalized anxiety, panic and social anxiety, but not in depression and separation anxiety. Separation anxiety was characterized by particularly high change in genetic influences over time.

Non-shared environmental influences on all symptoms were largely age-specific. For example, the non-shared environmental factors influencing generalized anxiety symptoms at age 15 had a small effect at age 17, and no significant effect at age 20. For 95% confidence intervals see Table B1.

Heterotypic continuity

In the common pathway model the total variance in each variable is explained by the latent factor and the variable-specific influences. Stable influences accounted for 21-69% of the variance in each variable (L^2, see Table 4.2 footnote) and were largely influenced by genes

(A_l=.61-.76), with the remaining variance explained by modest to moderate, significant non-shared environmental influences (E_l=.24-.39) (Table 4.2). The latent factors were generally highly correlated (r_{phl}=.58-.83) (Table 4.3). Genetic influences on latent factors overlapped considerably (r_{Al}=.60-.86) and the non-shared environmental correlations between the latent factors were also high (r_{El}=.46-.76) (*Table 4.3*). The variable-specific genetic influences were small (A_s=.01-.26) (Table 4.2), since most of the genetic influences acted via the latent factors. Conversely, variable-specific non-shared environmental influences were moderate (E_s=.31-.56) and accounted for most of the non-shared environmental influences on each variable (Table 4.2). The phenotypic within-time correlations between the variable-specific influences varied widely (r_{phs}=-.12-.56), as did the genetic and non-shared environmental within-time correlations between them (Table 4.3).

Model fit statistics for comparisons to the saturated models, and testing whether parameters can be dropped, are presented in Table B2. Model fit statistics corroborate AE models and in the full models C estimates are very small. However, for completeness full ACE models are presented in supplementary materials (Tables B3-5). Full ACE Cholesky decompositions suggest smaller genetic innovation than AE models (Table B3). Otherwise dropping C from the models did not have impact on the interpretation of the results. The within-time analyses of these variables, including univariate ACE results, are presented elsewhere (Lau, Gregory, Goldwin, Pine, & Eley, 2007; Waszczuk et al., 2014). The longitudinal association between depression at times 1 and 2 was also reported previously (Lau & Eley, 2006).

4.5. Discussion

The current study is the first to investigate, using quantitative genetics approach, how etiological influences contribute to developmental stability and change of depression, four anxiety symptom clusters, and their co-occurrence across adolescence and young adulthood. The results provide support for largely stable and broad genetic influences accounting for co-

occurrence and continuity over time. Environmental influences were generally more specific to time and symptom scales, contributing to change in symptoms over time.

Homotypic continuity

Genetic influences on symptoms stability

Moderate homotypic continuity of depression and each anxiety symptom scale across the five year period was observed, as expected (Costello et al., 2003; Gregory et al., 2007; Rutter et al., 2006). We found that stable genetic influences largely underpinned this continuity, in agreement with previous research that suggests strong genetic stability across development (Garcia et al., 2013; Gillespie et al., 2004; O'Connor et al., 1998; Trzaskowski et al., 2011; Waszczuk et al., 2013).

Environmental and genetic influences on symptoms change

The non-shared environmental influences on homotypic continuity of each symptom were largely time-specific, as expected (Bartels et al., 2004; Garcia et al., 2013; Haberstick et al., 2005; Lau & Eley, 2006; Lewis & Plomin, 2015; Scourfield et al., 2003; van der Valk et al., 2003; Zavos et al., 2012). Furthermore, we found new genetic influences emerged over time (genetic innovation (Kendler, Gardner, Annas, et al., 2008)) and previous genetic influences gradually declined over time (genetic attenuation), in agreement with other findings (Bartels et al., 2004; Haberstick et al., 2005; Kendler, Gardner, Annas, et al., 2008; Kendler, Gardner, & Lichtenstein, 2008; Lau & Eley, 2006; Lewis & Plomin, 2015; Nivard et al., 2014; Scourfield et al., 2003; van der Valk et al., 2003; Zavos et al., 2012). These newly emerging, developmentally dynamic environmental and genetic effects can contribute to change in the course of depression and anxiety symptoms.

The current study extends previous findings by investigating longitudinal etiological influences on homotypic continuity of depression and anxiety symptoms scales separately. A similar pattern of substantial genetic stability and largely time-specific environmental influences was

observed on all symptoms, possibly due to a substantial overlap between the genes influencing depression and anxiety (Eley & Stevenson, 1999; Kendler et al., 1987; Mosing et al., 2009; Thapar & McGuffin, 1997; Waszczuk et al., 2014; Zavos et al., 2012). However, some differences were notable. Depression, generalized and social anxiety symptoms showed more genetic stability than panic and separation anxiety symptoms, where genetic influences tended to attenuate more sharply, with proportionately greater genetic innovation at age 17 (panic and separation anxiety symptoms) and 20 years (separation anxiety symptoms). This might reflect relatively late median age of onset of panic disorder (Costello et al., 2003; Kessler, Berglund, et al., 2005), and that pediatric and adult-onset separation anxiety might differ considerably (Costello, Copeland, & Angold, 2011; Shear, Jin, Ruscio, Walters, & Kessler, 2006).

Heterotypic continuity

Genetic influences on symptoms stability

Heterotypic continuity across the symptom scales was significant, reflecting high comorbidity between depression and anxiety symptoms (Costello et al., 2003; Ferdinand et al., 2007; Goodwin et al., 2004; Gregory et al., 2007; Merikangas, 1993; Moffitt et al., 2007; Pine et al., 2001; Rutter et al., 2006; Spatola et al., 2007; Trzaskowski et al., 2011). This longitudinal comorbidity was largely explained by genetic overlap between the stable genetic influences that contribute to chronicity of each disorder, as well as overlap between the time-specific genetic influences. The time-specific influences represent developmentally dynamic genes that operate across short time periods and might reflect genes that come online in late adolescence or young adulthood. The current study provides preliminary evidence that both stable and time-specific genetic influences have general effects (i.e. on both depression and anxiety) (Eley, 1997), contributing to the enduring high genetic overlap between the symptom scales over time. These results carry implications for molecular genetic studies of depression and anxiety that aim to identify specific genetic variants involved in these disorders. They provide preliminary support for broadening the phenotypes included in molecular genetic studies, to

increase power to detect shared susceptibility loci for a range of internalizing symptoms (Hettema, Chen, Sun, & Brown, 2015; O'Reilly et al., 2012). However, the developmentally dynamic nature of genetic influences, in particular the genetic attenuation and innovation seen in adolescence suggests that stratifying sample collection by age may reduce heterogeneity (Traylor, Markus, & Lewis, 2014; Zaitlen et al., 2012). Identifying specific genes or polygenic risk scores may in turn inform clinical interventions, for example by using genetic markers to predict pharmacological or psychological treatment response (Eley et al., 2012; Keers & Aitchison, 2011; Lester & Eley, 2013).

Environmental influences on symptoms change and stability

As expected, environmental influences were largely time- and symptom-specific, thus contributing to the *change* in comorbidity over time. However, a modest proportion of environmental influences contributed significantly to the stability of each symptom scale, albeit to a lesser extent than the genetic influences. The results are in line with some previous findings (Kendler, Gardner, Annas, et al., 2008; Nivard et al., 2014; O'Connor et al., 1998), and extend them by showing that these stable non-shared environmental influences overlap considerably between depression and anxiety symptom scales, contributing to longitudinal comorbidity. The results indicate that some environmental influences play a significant role in maintenance of depression and anxiety alongside genetic influences, possibly by producing enduring effects though biological and social changes in an individual (Kendler et al., 2011). These enduring environmental influences have an impact on a wide range of outcomes. These may include effects of severe environmental stressors such as childhood maltreatment or natural disasters (Anda et al., 2006; Asselmann, Wittchen, Lieb, Höfler, & Beesdo-Baum, 2015; Goenjian et al., 2005; Kendler et al., 2000). Future studies should identify the life events that operate in this stable and broad manner to inform transdiagnostic interventions and prevention strategies (Barlow, Allen, & Choate, 2004; Clark & Taylor, 2009; Krueger & Eaton,

2015; McEvoy, Nathan, & Norton, 2009; Weersing, Rozenman, Maher-Bridge, & Campo, 2012; Wilamowska et al., 2010).

Limitations

The genetically-informative, representative sample and multiple time points are strengths of the current study. However, a number of limitations are noteworthy. First, our analyses used only self-report symptom scales and the results should be replicated in clinical samples with comorbid diagnoses and using lifetime diagnostic interviews. This approach was taken because clinical levels of internalizing disorders are rare in general adolescent population and questionnaires might capture less severe symptoms of these disorders, for example self-reported panic might capture physical symptoms of anxiety rather than panic attacks. However, symptoms of internalizing disorders are important markers of psychopathology (Balázs et al., 2013; Fergusson, Horwood, Ridder, & Beautrais, 2005; Pickles et al., 2001). Common mental disorders are now considered to be the extremes of quantitative traits (Insel et al., 2010; Plomin, Haworth, & Davis, 2009) and there is evidence that differently defined internalizing problems have the same etiology (Kendler et al., 1987; Kendler, Neale, Kessler, Heath, & Eaves, 1992a, 1992b). Second, at time 3 a different anxiety questionnaire was used reflecting the participants' older age. However, the longitudinal associations suggest a comparable continuity of the scores within and across different measures, in line with the view that they measure the same underlying constructs. Third, there was attrition in the sample. Although attrition bias might complicate estimation of trait prevalence, it is unlikely to affect the estimation of between trait associations (Wolke et al., 2009). Fourth, we did not measure other anxiety symptoms such as phobias, and future research should extend our findings to a wider range of internalizing symptoms. Fifth, future work should explore other types of continuity that were not addressed here, such as continuity across diagnoses. Last, there are limitations inherent to the twin design, discussed comprehensively elsewhere (Plomin,

DeFries, McClearn, & McGuffin, 2008). These have minimal and contrasting effects on parameter estimates which should be taken as indicative rather than absolute.

Conclusions

Our results suggest that both homotypic and heterotypic continuity of depression and anxiety symptoms across adolescence and young adulthood is underpinned largely by stable genetic influences, while non-shared environmental effects tend to be time- and symptom-specific. The results have multiple implications for future molecular genetics research and clinical practice in the context of comorbidity. They affirm the need to continue examining how the risk and maintenance factors for internalizing psychopathology operate across development to inform successful prevention and intervention strategies.

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Monika A. Waszczuk had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

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4.7. REFERENCES

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders, DSM-5* (Fifth ed.). Arlington, VA: American Psychiatric Publishing.

Anda, R. F., Felitti, V. J., Bremner, J. D., Walker, J. D., Whitfield, C., Perry, B. D., . . . Giles, W. H. (2006). The enduring effects of abuse and related adverse experiences in childhood. *European Archives of Psychiatry and Clinical Neuroscience, 256*(3), 174-186.

Angold, A., Costello, E. J., & Erkanli, A. (1999). Comorbidity. *Journal of Child Psychology and Psychiatry, 40*(1), 57-87.

Angold, A., Costello, E. J., Messer, S. C., Pickles, A., Winder, F., & Silver, D. (1995). The development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. *International Journal of Methods in Psychiatric Research, 5*, 1-12.

Asselmann, E., Wittchen, H.-U., Lieb, R., Höfler, M., & Beesdo-Baum, K. (2015). Danger and loss events and the incidence of anxiety and depressive disorders: a prospective-longitudinal community study of adolescents and young adults. *Psychological Medicine, 45*, 153–163.

Axelson, D. A., & Birmaher, B. (2001). Relation between anxiety and depressive disorders in childhood and adolescence. *Depression and Anxiety, 14*(2), 67-78.

Balázs, J., Miklósi, M., Keresztény, Á., Hoven, C. W., Carli, V., Wasserman, C., . . . Cosman, D. (2013). Adolescent subthreshold-depression and anxiety: psychopathology, functional impairment and increased suicide risk. *Journal of Child Psychology and Psychiatry, 54*(6), 670-677.

Barlow, D. H., Allen, L. B., & Choate, M. L. (2004). Toward a unified treatment for emotional disorders. *Behavior Therapy, 35*(2), 205-230.

Bartels, M., van den Oord, E. J., Hudziak, J. J., Rietveld, M. J., Van Beijsterveldt, C. E., & Boomsma, D. I. (2004). Genetic and environmental mechanisms underlying stability

and change in problem behaviors at ages 3, 7, 10, and 12. *Developmental Psychology, 40*(5), 852-867.

Beesdo, K., Knappe, S., & Pine, D. S. (2009). Anxiety and anxiety disorders in children and adolescents: developmental issues and implications for DSM-V. *Pediatric Clinics of North America, 32*(3), 483-524.

Beesdo, K., Pine, D. S., Lieb, R., & Wittchen, H. (2010). Incidence and risk patterns of anxiety and depressive disorders and categorization of generalized anxiety disorder. *Archives of General Psychiatry, 67*(1), 47-57.

Bergen, S. E., Gardner, C. O., & Kendler, K. S. (2007). Age-related changes in heritability of behavioral phenotypes over adolescence and young adulthood: a meta-analysis. *Twin Research & Human Genetics, 10*(3), 423-433.

Birmaher, B., Brent, D. A., Chiappetta, L., Bridge, J., Monga, S., & Baugher, M. (1999). Psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED): a replication study. *Journal of the American Academy of Child & Adolescent Psychiatry, 38*(10), 1230-1236.

Blakemore, S.-J. (2008). The social brain in adolescence. *Nature Reviews: Neuroscience, 9*(4), 267-277.

Boker, S., Neale, M., Maes, H., Wilde, M., Spiegel, M., Brick, T., . . . Bates, T. (2011). OpenMx: an open source extended structural equation modeling framework. *Psychometrika, 76*(2), 306-317.

Chorpita, B. F., Yim, L., Moffitt, C., Umemoto, L. A., & Francis, S. E. (2000). Assessment of symptoms of DSM-IV anxiety and depression in children: A revised child anxiety and depression scale. *Behaviour Research and Therapy, 38*(8), 835-855.

Clark, D. A., & Taylor, S. (2009). The transdiagnostic perspective on cognitive-behavioral therapy for anxiety and depression: New wine for old wineskins? *Journal of Cognitive Psychotherapy, 23*(1), 60-66.

Costello, E. J., Copeland, W., & Angold, A. (2011). Trends in psychopathology across the adolescent years: What changes when children become adolescents, and when adolescents become adults? *Journal of child psychology and psychiatry, 52*(10), 1015-1025.

Costello, E. J., Mustillo, S., Erkanli, A., Keeler, G., & Angold, A. (2003). Prevalence and development of psychiatric disorders in childhood and adolescence. *Archives of General Psychiatry, 60*(8), 837-844.

Eley, T. C. (1997). General genes: A new theme in developmental psychopathology. *Current Directions in Psychological Science, 6*, 90-95.

Eley, T. C., Hudson, J. L., Creswell, C., Tropeano, M., Lester, K. J., Cooper, P., . . . Collier, D. A. (2012). Therapygenetics: the 5HTTLPR and response to psychological therapy. *Molecular Psychiatry, 17*(3), 236-237.

Eley, T. C., & Stevenson, J. (1999). Using genetic analyses to clarify the distinction between depressive and anxious symptoms in children and adolescents. *Journal of Abnormal Child Psychology, 27*(2), 105-114.

Ferdinand, R. F., Dieleman, G., Ormel, J., & Verhulst, F. C. (2007). Homotypic versus heterotypic continuity of anxiety symptoms in young adolescents: evidence for distinctions between DSM-IV subtypes. *Journal of Abnormal Child Psychology, 35*(3), 325-333.

Fergusson, D. M., Horwood, L. J., Ridder, E. M., & Beautrais, A. L. (2005). Subthreshold depression in adolescence and mental health outcomes in adulthood. *Archives of General Psychiatry, 62*(1), 66-72.

Garcia, S. E., Tully, E. C., Tarantino, N., South, S., Iacono, W. G., & McGue, M. (2013). Changes in genetic and environmental influences on trait anxiety from middle adolescence to early adulthood. *Journal of Affective Disorders, 151*(1), 46-53.

Gillespie, N. A., Kirk, K. M., Evans, D. M., Heath, A. C., Hickie, I. B., & Martin, N. G. (2004). Do the genetic or environmental determinants of anxiety and depression change with age? A longitudinal study of Australian twins. *Twin Research, 7*(01), 39-53.

Goenjian, A. K., Walling, D., Steinberg, A. M., Karayan, I., Najarian, L. M., & Pynoos, R. (2005). A prospective study of posttraumatic stress and depressive reactions among treated and untreated adolescents 5 years after a catastrophic disaster. *American Journal of Psychiatry, 162*(12), 2302-2308.

Goldberg, D. (2008). Towards DSM-V: the relationship between generalized anxiety disorder and major depressive episode. *Psychological Medicine, 38*(11), 1671 - 1675.

Goodwin, R. D., Fergusson, D. M., & Horwood, L. J. (2004). Early anxious/withdrawn behaviours predict later internalising disorders. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 45*(4), 874-883.

Gregory, A. M., Buysse, D. J., Willis, T. A., Rijsdijk, F. V., Maughan, B., Rowe, R., . . . Eley, T. C. (2011). Associations between sleep quality and anxiety and depression symptoms in a sample of young adult twins and siblings. *Journal of Psychosomatic Research, 71*, 250-255. doi: 10.1016/j.jpsychores.2011.03.011

Gregory, A. M., Caspi, A., Moffitt, T. E., Koenen, K., Eley, T. C., & Poulton, R. (2007). Juvenile mental health histories of adults with anxiety disorders. *American Journal of Psychiatry, 164*(2), 301-308.

Haberstick, B. C., Schmitz, S., Young, S. E., & Hewitt, J. K. (2005). Contributions of genes and environments to stability and change in externalizing and internalizing problems during elementary and middle school. *Behavior Genetics, 35*(4), 381-396.

Hettema, J., Chen, X., Sun, C., & Brown, T. (2015). Direct, indirect and pleiotropic effects of candidate genes on internalizing disorder psychopathology. *Psychological Medicine*, 1-10.

Hettema, J. M. (2008). The nosologic relationship between generalized anxiety disorder and major depression. *Depression and Anxiety, 25*(4), 300-316.

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., . . . Wang, P. (2010). Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *American Journal of Psychiatry, 167*(7), 748-751.

Kadosh, K. C., Linden, D. E., & Lau, J. Y. (2013). Plasticity during childhood and adolescence: innovative approaches to investigating neurocognitive development. *Developmental Science, 16*(4), 574-583.

Keers, R., & Aitchison, K. J. (2011). Pharmacogenetics of antidepressant response. *Expert Review of Neurotherapeutics, 11*(1), 101-125.

Kendler, K. S., Bulik, C. M., Silberg, J., Hettema, J. M., Myers, J., & Prescott, C. A. (2000). Childhood sexual abuse and adult psychiatric and substance use disorders in women: an epidemiological and cotwin control analysis. *Archives of General Psychiatry, 57*(10), 953-959.

Kendler, K. S., Eaves, L. J., Loken, E. K., Pedersen, N. L., Middeldorp, C. M., Reynolds, C., . . . Gardner, C. O. (2011). The impact of environmental experiences on symptoms of anxiety and depression across the life span. *Psychological Science, 22*(10), 1343-1352.

Kendler, K. S., Gardner, C. O., Annas, P., Neale, M. C., Eaves, L. J., & Lichtenstein, P. (2008). A longitudinal twin study of fears from middle childhood to early adulthood: evidence for a developmentally dynamic genome. *Archives of General Psychiatry, 65*(4), 421-429.

Kendler, K. S., Gardner, C. O., & Lichtenstein, P. (2008). A developmental twin study of symptoms of anxiety and depression: evidence for genetic innovation and attenuation. *Psychological Medicine, 38*(11), 1567-1575.

Kendler, K. S., Heath, A. C., Martin, N. G., & Eaves, L. J. (1987). Symptoms of anxiety and symptoms of depression. Same genes, different environments? *Archives of General Psychiatry, 44*(5), 451-457.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1992a). Major depression and generalized anxiety disorder. Same genes, (partly) different environments? *Archives of General Psychiatry, 49*(9), 716-722.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1992b). A population-based twin study of major depression in women. The impact of varying definitions of illness. *Archives of General Psychiatry, 49*(4), 257-266.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*(6), 593-602.

Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*(6), 617-627.

Krueger, R. F., & Eaton, N. R. (2015). Transdiagnostic factors of mental disorders. *World Psychiatry, 14*(1), 27-29.

Lahey, B. B., Zald, D. H., Hakes, J. K., Krueger, R. F., & Rathouz, P. J. (2014). Patterns of heterotypic continuity associated with the cross-sectional correlational structure of prevalent mental disorders in adults. *JAMA Psychiatry, 71*(9), 989-996.

Lau, J. Y. F., & Eley, T. C. (2006). Changes in genetic and environmental influences on depressive symptoms across adolescence and young adulthood. *British Journal of Psychiatry, 189*(5), 422-427.

Lau, J. Y. F., Gregory, A. M., Goldwin, M. A., Pine, D. S., & Eley, T. C. (2007). Assessing gene-environment interactions on anxiety symptom subtypes across childhood and adolescence. *Development and Psychopathology, 19*, 1129-1146.

Lester, K. J., & Eley, T. C. (2013). Therapygenetics: Using genetic markers to predict response to psychological treatment for mood and anxiety disorders. *Biology of mood & anxiety disorders, 3*(4), 1-16.

Lewis, G. J., & Plomin, R. (2015). Heritable influences on behavioural problems from early childhood to mid-adolescence: evidence for genetic stability and innovation. *Psychological Medicine, FirstView Article*.

McAdams, T. A., Gregory, A. M., Rowe, R., Zavos, H., Barclay, N. L., Lau, J. Y., . . . Eley, T. C. (2013). The genesis 12–19 (G1219) study: a twin and sibling study of gene–environment interplay and adolescent development in the UK. *Twin Research & Human Genetics, 1*(1), 1-10.

McEvoy, P. M., Nathan, P., & Norton, P. J. (2009). Efficacy of transdiagnostic treatments: A review of published outcome studies and future research directions. *Journal of Cognitive Psychotherapy, 23*(1), 20-33.

McGue, M., & Bouchard, T. J., Jr. (1984). Adjustment of twin data for the effects of age and sex. *Behavior Genetics, 14*(4), 325-343.

Mennin, D. S., Heimberg, R. G., Fresco, D. M., & Ritter, M. R. (2008). Is generalized anxiety disorder an anxiety or mood disorder? Considering multiple factors as we ponder the fate of GAD. *Depression and Anxiety, 25*(4), 289-299.

Merikangas, K. R. (1993). Genetic epidemiologic studies of affective disorders in childhood and adolescence. *European Archives of Psychiatry and Clinical Neuroscience, 243*, 121-130.

Moffitt, T. E., Harrington, H., Caspi, A., Kim-Cohen, J., Goldberg, D., Gregory, A. M., & Poulton, R. (2007). Depression and generalized anxiety disorder: cumulative and sequential comorbidity in a birth cohort followed prospectively to age 32 years. *Archives of General Psychiatry, 64*(6), 651-660.

Mosing, M. A., Gordon, S. D., Medland, S. E., Statham, D. J., Nelson, E. C., Heath, A. C., . . . Wray, N. R. (2009). Genetic and environmental influences on the co-morbidity between depression, panic disorder, agoraphobia, and social phobia: a twin study. *Depression and Anxiety, 26*(11), 1004-1011.

Nivard, M., Dolan, C., Kendler, K., Kan, K., Willemsen, G., van Beijsterveldt, C., . . . Bartels, M. (2014). Stability in symptoms of anxiety and depression as a function of genotype and environment: a longitudinal twin study from ages 3 to 63 years. *Psychological Medicine*, 1-11.

O'Connor, T. G., Neiderhiser, J. M., Reiss, D., Hetherington, E. M., & Plomin, R. (1998). Genetic contributions to continuity, change, and co-occurrence of antisocial and depressive symptoms in Adolescence. *Journal of Child Psychology and Psychiatry, 39*, 323-336.

O'Reilly, P. F., Hoggart, C. J., Pomyen, Y., Calboli, F. C., Elliott, P., Jarvelin, M.-R., & Coin, L. J. (2012). MultiPhen: joint model of multiple phenotypes can increase discovery in GWAS. *PLoS ONE, 7*(5), e34861.

Pickles, A., Rowe, R., Simonoff, E., Foley, D., Rutter, M., & Silberg, J. (2001). Child psychiatric symptoms and psychosocial impairment: relationship and prognostic significance. *British Journal of Psychiatry, 179*, 230-235.

Pine, D. S., Cohen, P., & Brook, J. (2001). Adolescent fears as predictors of depression. *Biological Psychiatry, 50*(9), 721-724.

Plomin, R., DeFries, J. C., Knopik, V. S., & Neiderhiser, J. M. (2013). *Behavioral Genetics* (6th ed.). New York: Worth Publishers.

Plomin, R., DeFries, J. C., McClearn, G. E., & McGuffin, P. (2008). *Behavioral genetics*. New York: Worth Publishers.

Plomin, R., Haworth, C. M., & Davis, O. S. (2009). Common disorders are quantitative traits. *Nature Reviews: Genetics, 10*(12), 872-878.

Rapee, R. M., Schniering, C. A., & Hudson, J. L. (2009). Anxiety Disorders During Childhood and Adolescence: Origins and Treatment. *Annual Review of Clinical Psychology, 5*, 311-341.

Rijsdijk, F. V., & Sham, P. C. (2002). Analytic approaches to twin data using structural equation models. *Briefings in bioinformatics, 3* 119-133.

Roberson-Nay, R., Eaves, L. J., Hettema, J. M., Kendler, K. S., & Silberg, J. L. (2012). Childhood separation anxiety disorder and adult onset panic attacks share a common genetic diathesis. *Depression and anxiety, 29*(4), 320-327.

Rutter, M., Kim-Cohen, J., & Maughan, B. (2006). Continuities and discontinuities in psychopathology between childhood and adult life. *Journal of Child Psychology and Psychiatry, 47*, 276-295.

Schmitz, S., Fulker, D. W., & Mrazek, D. (1995). Problem behavior in early and middle childhood: An initial behavior genetic analysis. *Journal of Child Psychology and Psychiatry, 36*(8), 1443-1458.

Scourfield, J., Rice, F., Thapar, A., Harold, G. T., Martin, N., & McGuffin, P. (2003). Depressive symptoms in children and adolescents: changing aetiological influences with development. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 44*(7), 968-976.

Shear, K., Jin, R., Ruscio, A., Walters, E., & Kessler, R. (2006). Prevalence and correlates of estimated DSM-IV child and adult separation anxiety disorder in the National Comorbidity Survey Replication. *American Journal of Psychiatry, 163*(6), 1074-1083.

Silberg, J. L., Rutter, M., & Eaves, L. (2001). Genetic and environmental influences on the temporal association between earlier anxiety and later depression in girls. [erratum appears in Biol Psychiatry 2001 Sep 1;50(5):393.]. *Biological Psychiatry, 49*(12), 1040-1049.

Spatola, C. A., Fagnani, C., Pesenti-Gritti, P., Ogliari, A., Stazi, M. A., & Battaglia, M. (2007). A general population twin study of the CBCL/6-18 DSM-oriented scales. *Journal of the American Academy of Child & Adolescent Psychiatry, 46*(5), 619-627.

Spence, S. H. (1997). Structure of anxiety symptoms among children: A confirmatory factor-analytic study. *Journal of Abnormal Psychology, 106*, 280-297.

Spence, S. H. (1998). A measure of anxiety symptoms among children. *Behaviour Research & Therapy, 36*(5), 545-566.

TeamRDC. (2010). R: A Language and Environment for Statistical Computing. *R Foundation for Statistical Computing. Vienna Austria.*

Thapar, A., & McGuffin, P. (1997). Anxiety and depressive symptoms in childhood - a genetic study of comorbidity. *Journal of Child Psychology and Psychiatry, 38*(6), 651-656.

Traylor, M., Markus, H., & Lewis, C. M. (2014). Homogeneous case subgroups increase power in genetic association studies. *European Journal of Human Genetics*, 1-7.

Trzaskowski, M., Zavos, H., Haworth, C., Plomin, R., & Eley, T. (2011). Stable Genetic Influence on Anxiety-Related Behaviours Across Middle Childhood. *Journal of Abnormal Child Psychology, 40*(1), 85-94.

van der Valk, J. C., van den Oord, E. J., Verhulst, F. C., & Boomsma, D. I. (2003). Genetic and environmental contributions to stability and change in children's internalizing and externalizing problems. *Journal of the American Academy of Child & Adolescent Psychiatry, 42*(10), 1212-1220.

Wagenmakers, E.-J., & Farrell, S. (2004). AIC model selection using Akaike weights. *Psychonomic bulletin & review, 11*(1), 192-196.

Waszczuk, M. A., Zavos, H. M. S., & Eley, T. C. (2013). Genetic and Environmental Influences on Relationship between Anxiety Sensitivity and Anxiety Subscales in Children. *Journal of Anxiety Disorders, 27*(5), 475-484.

Waszczuk, M. A., Zavos, H. M. S., Gregory, A. M., & Eley, T. C. (2014). The phenotypic and etiological structure of depression and anxiety disorder symptoms in childhood, adolescence and young adulthood. *JAMA Psychiatry, 71*(8), 905-916.

Weersing, V. R., Rozenman, M. S., Maher-Bridge, M., & Campo, J. V. (2012). Anxiety, depression, and somatic distress: Developing a transdiagnostic internalizing toolbox for pediatric practice. *Cognitive and behavioral practice, 19*(1), 68-82.

Wilamowska, Z. A., Thompson-Hollands, J., Fairholme, C. P., Ellard, K. K., Farchione, T. J., & Barlow, D. H. (2010). Conceptual background, development, and preliminary data from the unified protocol for transdiagnostic treatment of emotional disorders. *Depression and Anxiety, 27*(10), 882-890.

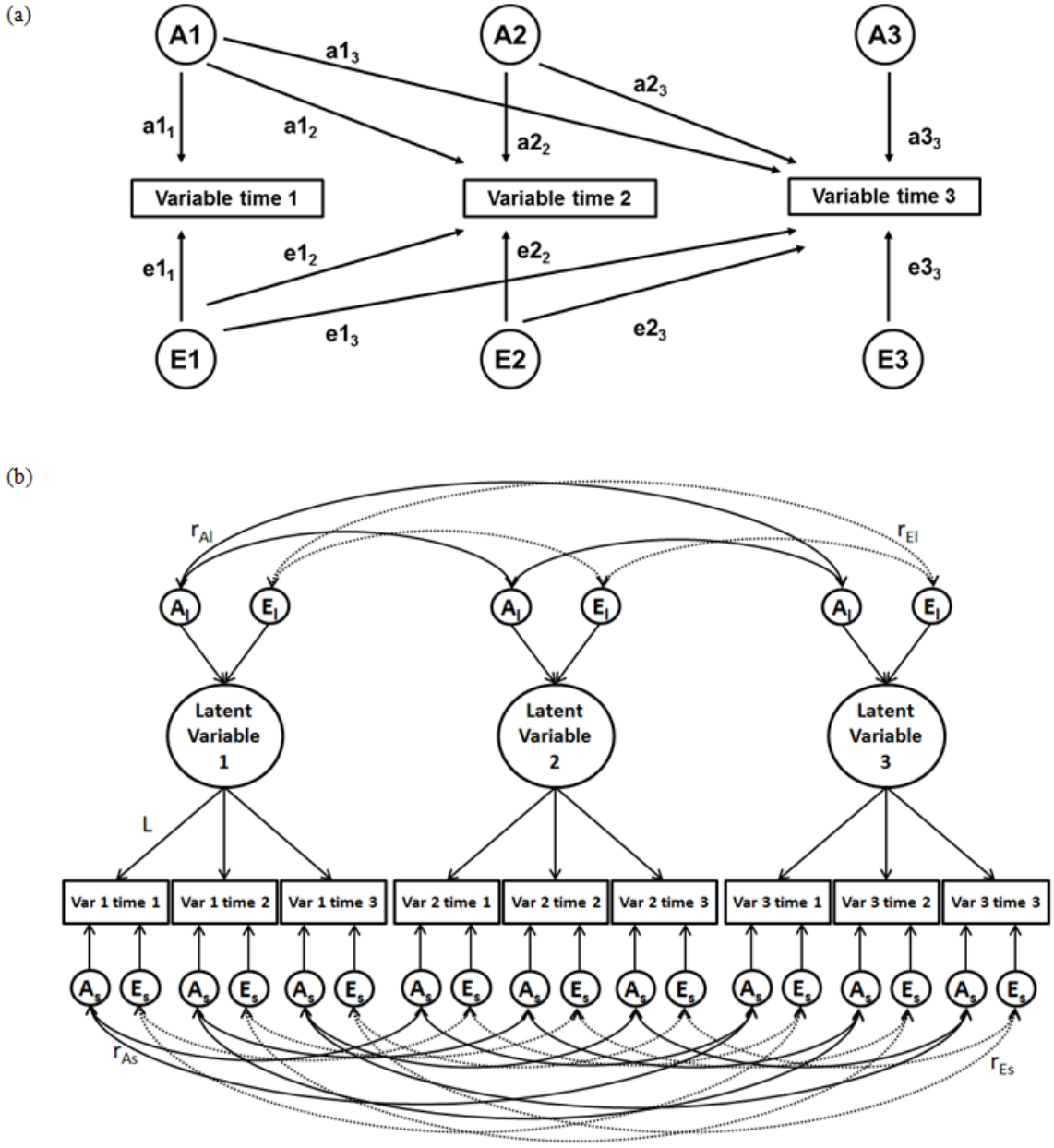
Wolke, D., Waylen, A., Samara, M., Steer, C., Goodman, R., Ford, T., & Lamberts, K. (2009). Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders. *The British Journal of Psychiatry, 195*(3), 249-256.

Yurgelun-Todd, D. (2007). Emotional and cognitive changes during adolescence. *Current Opinion in Neurobiology, 17*(2), 251-257.

Zaitlen, N., Lindström, S., Pasaniuc, B., Cornelis, M., Genovese, G., Pollack, S., . . . Eyre, S. (2012). Informed conditioning on clinical covariates increases power in case-control association studies. *PLoS Genetics, 8*(11), e1003032.

Zavos, H. M. S., Rijsdijk, F. V., & Eley, T. C. (2012). A Longitudinal, Genetically Informative, Study of Associations Between Anxiety Sensitivity, Anxiety and Depression. *Behavior Genetics, 42*(4), 592-602.

Figure 4.1 - Multivariate models: (a) longitudinal Cholesky decomposition, (b) Common pathway model



Notes:

A - additive genetic effects; *E* - non-shared environmental effects, *Var* – variable. Subscript 'l' denotes stable influences on the latent factor, subscript 's' denotes variable- and time-specific influences.

Figure 4.1 (continued) – Multivariate models: (a) longitudinal Cholesky decomposition, (b) Common pathway model

In Figure 4.1(a), variance paths, which must be squared to estimate the proportion of variance accounted for, are represented by lowercase letters and followed by two numerals, e.g. $a1_1$, $c2_2$, $e3_3$.

In Figure 4.1(b), only three variables are presented for clarity; however the model was run with all five variables included, each measured at three time points.

Figure 4.2 - Longitudinal Cholesky decomposition results: The proportion of total variance in depression and anxiety symptom scales accounted for by genetic and non-shared environmental influences.

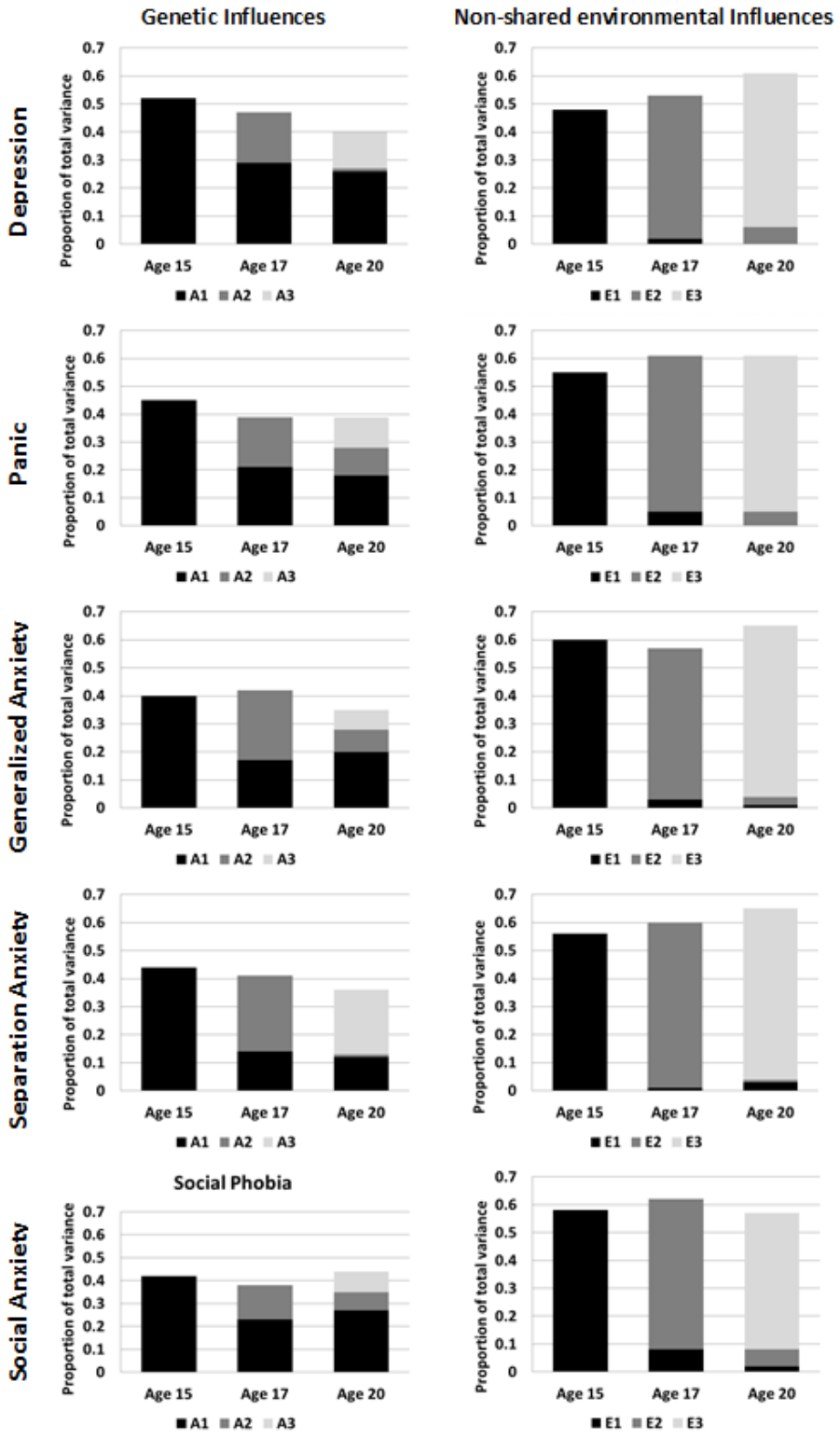


Figure 4.2 (continued) – Longitudinal Cholesky decomposition results: The proportion of total variance in depression and anxiety symptom scales accounted for by genetic and non-shared environmental influences.

Notes:

A – additive genetic effects, *E*-non-shared environmental influences. Mean ages provided in the x-axis.

The y-axis represents the total phenotypic variance so the sum of all the factors equals the total heritability/non-shared environmental influences. The first genetic/non-shared environmental factor (A1/E1), which influences a variable at mean age 15, is represented in black. A dark grey represents the second genetic/non-shared environmental factor (A2/E2) that stars at mean age 17 years and the pale grey represents the third genetic/ non-shared environmental factor (A3/E3) that emerges at mean age 20 years.

The 95% confidence intervals are presented in *Table B1*.

AE models are presented, as C influences were not significant and were dropped from the multivariate models without a significant deterioration of the fit (*Table B2*). The AIC values suggest that dropping C lead to improvement of the model fit at these three waves. Full ACE results are presented in Tables B3-5 for completeness.

Table 4.1 - Longitudinal phenotypic correlations

	Depression	Panic	Generalized Anxiety	Separation Anxiety	Social Anxiety
Time 2 (17 years)			Time 1 (15 years)		
Depression	**.47 (.43-.51)**	.33 (.29-.37)	.31 (.27-.35)	.24 (.19-.29)	.30 (.26-.34)
Panic	.31 (.27-.35)	**.43 (.39-.47)**	.32 (.28-.36)	.24 (.19-.29)	.21 (.16-.26)
Generalized Anxiety	.37 (.33-.41)	.39 (.35-.43)	**.47 (.43-.51)**	.37 (.33-.41)	.35 (.31-.39)
Separation Anxiety	.11 (.06-.16)	.22 (17-.27)	.22 (17-.27)	**.36 (.32-.40)**	.16 (.11-.21)
Social Anxiety	.29 (.24-.33)	.29 (.24-.33)	.34 (.30-.38)	.31 (.27-.35)	**.53 (.49-.56)**
Time 3 (20 years)			Time 1 (15 years)		
Depression	**.38 (.34-.42)**	.32 (.28-.36)	.26 (.21-31)	.24 (.19-.29)	.24 (.19-.29)
Panic	.30 (.26-.34)	**.39 (.35-.43)**	.36 (.32-.40)	.28 (.23-.33)	.26 (.21-.31)
Generalized Anxiety	.34 (.30-.38)	.33 (.29-.37)	**.36 (.32-.40)**	.35 (.31-.39)	.34 (.30-.38)
Separation Anxiety	.32 (.28-.36)	.40 (.36-.44)	.35 (.31-.39)	**.39 (.35-.43)**	.32 (.28-.36)
Social Anxiety	.33 (.29-.37)	.33 (.29-.37)	.38 (.34-.42)	.31 (.27-.35)	**.46 (.42-.50)**
Time 3 (20 years)			Time 2 (17 years)		
Depression	**.47 (.43-.51)**	.34 (.30-.38)	.38 (.34-.42)	.12 (.07-.18)	.31 (.27-.35)
Panic	.34 (.30-.38)	**.48 (.44-.52)**	.45 (.41-.49)	.21 (.16-.26)	.28 (.23-.33)
Generalized Anxiety	.39 (.35-.43)	.31 (.27-.35)	**.53 (.49-.56)**	.25 (.20-.30)	.40 (.36-.44)
Separation Anxiety	.35 (.31-.39)	.40 (.36-.44)	.46 (.42-.50)	**.35 (.31-.39)**	.36 (.32-.40)
Social Anxiety	.39 (.35-.43)	.30 (.26-.34)	.46 (.42-.50)	.17 (.12-.22)	**.58 (.54-.62)**

Notes:

Mean ages provided in the headings.

Homotypic continuity is presented on diagonal (in bold), heterotypic continuity across diagonal.

95% Confidence Intervals (CIs) are presented in brackets. CIs not inclusive of zeros indicate significant correlations. Non-overlapping CIs mean significant difference between the values.

Results presented on untransformed variables for comparison with other published samples. The within-time correlations between depression and anxiety subscales are discussed elsewhere (Lau et al., 2007; Waszczuk et al., 2014). The homotypic continuity of anxiety subscales has also previously been reported (Waszczuk et al., 2014).

Table 4.2 - Common pathway model results: Genetic and non-shared environmental influences on the latent factor, and latent factor and time-specific influences on each variable.

		Depression			Panic			Generalized Anxiety			Separation Anxiety			Social Anxiety		
Etiological influences on the latent factor	A_l	.76 (.65-.85)			.66 (.43-.77)			.64 (.51-.74)			.69 (.53-.83)			.61 (.51-.71)		
	E_l	.24 (.15-.35)			.34 (.23-.46)			.36 (.26-.49)			.31 (.17-.47)			.39 (.29-.49)		
Mean age		15	17	20	15	17	20	15	17	20	15	17	20	15	17	20
Latent factor influences on each variable	L	.63 (.58-.67)	.78 (.73-.83)	.58 (.52-.62)	.56 (.51-.61)	.71 (.66-.76)	.61 (.56-.66)	.57 (.52-.61)	.83 (.78-86)	.58 (.53-.63)	.55 (.50-.61)	.46 (.38-.52)	.60 (.54-.66)	.61 (.57-.65)	.82 (.78-.86)	.68 (.63-.72)
Time-specific etiological influences on each variable	A_s	.20 (.13-.27)	.03 (.00-.11)	.14 (.05-.23)	.17 (.10-.25)	.12 (.05-.21)	.07 (.00-.15)	.22 (.15-.30)	.01 (.00-.09)	.12 (.03-.21)	.21 (.13-.29)	.26 (.16-.36)	.11 (.02-.20)	.17 (.10-.24)	.02 (.00-.07)	.11 (.02-.20)
	E_s	.41 (.35-.47)	.36 (.28-.43)	.53 (.45-.63)	.51 (.44-.58)	.37 (.28-.46)	.56 (.47-.65)	.45 (.38-.53)	.31 (.22-.38)	.54 (.46-.63)	.48 (.41-.56)	.53 (.44-.64)	.53 (.44-.62)	.45 (.39-.53)	.31 (.24-.37)	.44 (.36-.52)

Notes:

A - additive genetic effects; E - non-shared environmental effects; L – Latent factor.

Table 4.2 (continued) – Common pathway model results: Genetic and non-shared environmental influences on the latent factor, and latent factor and time-specific influences on each variable.

Mean ages provided in the headings.

95% Confidence Intervals (CIs) are presented in brackets. CIs not inclusive of zeros indicate significant influences. Non-overlapping CIs mean significant difference between the values.

L needs to be squared to inform about the proportion of total variance accounted for by the latent factor. L^2 should be multiplied by A_l to obtain the proportion of the total variance due to the genetic influences from the latent factor. L^2 should be multiplied by E_l to obtain the proportion of the total variance due to the non-shared environmental influences from the latent factor. Total variance of a trait = $L^2 + A_s + E_s$

AE models are presented, as C influences were not significant and were dropped from the multivariate models without a significant deterioration of the fit (*Table B2*). The AIC values suggest that dropping C lead to improvement of the model fit at these three waves. Full ACE results are presented in Tables B3-5 for completeness.

Table 4.3 - Common pathway model results: Phenotypic, genetic and non-shared environmental correlations between the latent factors and time-specific influences at 15, 17 and 20 years

		Depression	Panic	Generalized Anxiety	Separation Anxiety
Latent Factors					
Panic	r_{phl}	.72 (.67-.76)			
	r_{Al}	.74 (.66-.83)			
	r_{El}	.67 (.46-.85)			
Generalized Anxiety	r_{phl}	.74 (.69-.79)	.83 (.79-.87)		
	r_{Al}	.81 (.73-.88)	.86 (.79-.94)		
	r_{El}	.60 (.41-.76)	.76 (.61-.89)		
Separation Anxiety	r_{phl}	.58 (.51-.65)	.76 (.70-.82)	.80 (.75-.85)	
	r_{Al}	.60 (.48-.71)	.78 (.67-.89)	.86 (.76-.96)	
	r_{El}	.55 (.29-.80)	.73 (.51-.95)	.70 (.50-.89)	
Social Anxiety	r_{phl}	.63 (.58-.68)	.62 (.56-.67)	.75 (.71-.79)	.65 (.59-.70)
	r_{Al}	.67 (.59-.76)	.68 (.57-.78)	.77 (.69-.85)	.75 (.64-.87)
	r_{El}	.56 (.37-.72)	.52 (.34-.67)	.71 (.58-.83)	.46 (.24-.65)
Time-specific influences at 15					
Panic	r_{phs}	.43 (.38-.48)			
	r_{As}	.80 (.59-.99)			
	r_{Es}	.28 (.19-.38)			
Generalized Anxiety	r_{phs}	.44 (.39-.48)	.49 (.44-.52)		
	r_{As}	.57 (.37-.74)	.56 (.32-.73)		
	r_{Es}	.38 (.28-.46)	.46 (.38-.53)		
Separation Anxiety	r_{phs}	.34 (.29-.39)	.40 (.36-.45)	.43 (.38-.48)	
	r_{As}	.40 (.15-.59)	.64 (.41-.86)	.58 (.38-.76)	
	r_{Es}	.31 (.22-.41)	.31 (.22-.40)	.36 (.27-.44)	
Social Anxiety	r_{phs}	.36 (.31-.41)	.37 (.32-.42)	.48 (.44-.52)	.46 (.42-.51)
	r_{As}	.61 (.38-.81)	.64 (.39-.88)	.81 (.62-.99)	.66 (.44-.86)
	r_{Es}	.26 (.16-.36)	.28 (.18-.37)	.35 (.25-.43)	.39 (.29-.47)
Time-specific influences at 17					
Panic	r_{phs}	.19 (.09-.28)			
	r_{As}	.41 (-1.00-1.00)			
	r_{Es}	.15 (.00-.30)			
Generalized Anxiety	r_{phs}	.27 (.16-.37)	.38 (.29-.47)		
	r_{As}	-.13 (1.00-1.00)	.85 (-1.00-1.00)		
	r_{Es}	.29 (.13-.41)	.38 (.23-.52)		
Separation Anxiety	r_{phs}	-.12 (-.20--.04)	.02 (-.06-.09)	.11 (.02-.20)	
	r_{As}	-.33 (-1.00-1.00)	-.16 (-.60-.20)	.04 (-1.00-1.00)	
	r_{Es}	-.08 (-.22-.05)	.09 (-.06-.23)	.13 (-.02-.27)	
Social Anxiety	r_{phs}	.12 (.01-.22)	.05 (-.06-.14)	.16 (.03-.27)	.03 (-.06-.11)
	r_{As}	-.45 (-1.00-1.00)	-.94 (-1.00- -.12)	-.76 (-1.00-1.00)	.48 (-.27-.99)
	r_{Es}	.17 (.03-.31)	.20 (.05-.33)	.20 (.06-.36)	-.05 (-.19-.09)
Time-specific influences at 20					
Panic	r_{phs}	.36 (.30-.42)			
	r_{As}	.72 (.05-1.00)			

	r_{Es}	.30 (.19-.40)			
Generalized Anxiety	r_{phs}	.42 (.37-.47)	.44 (.39-.49)		
	r_{As}	.45 (-.15-.79)	.48 (-.07-.98)		
	r_{Es}	.42 (.31-.51)	.44 (.35-.53)		
Separation Anxiety	r_{phs}	.38 (.32-.44)	.44 (.38-.50)	.47 (.41-.52)	
	r_{As}	.66 (.15-.98)	.61 (-.58-1.00)	.63 (-.01-.95)	
	r_{Es}	.32 (.21-.42)	.42 (.32-.52)	.43 (.33-.53)	
Social Anxiety	r_{phs}	.45 (.40-.50)	.47 (.41-.52)	.56 (.51-.61)	.43 (.37-.48)
	r_{As}	.74 (.31-.99)	.70 (-.25-1.00)	.69 (.13-.94)	.33 (-.43-.79)
	r_{Es}	.38 (.28-.48)	.43 (.34-.53)	.53 (.45-.62)	.45 (.34-.55)

Notes:

r_{phl} - Phenotypic correlations between the latent factors; r_{Al} - Genetic correlations between the latent factors; r_{El} – Non-shared environmental correlations between the latent factors; r_{phs} - Phenotypic correlations between the time-specific influences; r_{As} - Genetic correlations between the time-specific influences; r_{Es} – Non-shared environmental correlations between the time-specific influences.

95% Confidence Intervals (CIs) are presented in brackets. CIs not inclusive of zeros indicate significant correlations. Non-overlapping CIs mean significant difference between the values.

AE models are presented, as C influences were not significant and were dropped from the multivariate models without a significant deterioration of the fit (*Table B2*). The AIC values suggest that dropping C lead to improvement of the model fit at these three waves. Full ACE results are presented in Tables B3-5 for completeness.

5. CHAPTER 5 - COGNITIVE CONTENT-SPECIFICITY IN ANXIETY AND DEPRESSIVE DISORDER SYMPTOMS: A TWIN STUDY OF CROSS-SECTIONAL ASSOCIATIONS WITH ANXIETY SENSITIVITY DIMENSIONS ACROSS DEVELOPMENT.

This chapter is presented as a published paper and is an exact copy of the following journal publication:

Brown, H. M.*, **Waszczuk, M. A.***, Zavos, H. M. S., Trzaskowski, M., Gregory, A. M., & Eley, T. C. (2014). Cognitive content-specificity in anxiety and depressive disorder symptoms: a twin study of cross-sectional associations with anxiety sensitivity dimensions across development. *Psychological Medicine, 44*(16), 3469-3480.

* Joint first authors contributed equally

Supplementary materials for this chapter are presented in **Appendix C**

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ORIGINAL ARTICLE

Cognitive content specificity in anxiety and depressive disorder symptoms: a twin study of cross-sectional associations with anxiety sensitivity dimensions across development

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Background. The classification of anxiety and depressive disorders has long been debated and has important clinical implications. The present study combined a genetically sensitive design and multiple time points to investigate cognitive content specificity in anxiety and depressive disorder symptoms across anxiety sensitivity dimensions, a cognitive distortion implicated in both disorders.

Method. Phenotypic and genetic correlations between anxiety sensitivity dimensions, anxiety and depressive disorder symptoms were examined at five waves of data collection within childhood, adolescence and early adulthood in two representative twin studies (*n* pairs=300 and 1372).

Results. The physical concerns dimension of anxiety sensitivity (fear of bodily symptoms) was significantly associated with anxiety but not depression at all waves. Genetic influences on physical concerns overlapped substantially more with anxiety than depression. Conversely, mental concerns (worry regarding cognitive control) were phenotypically more strongly associated with depression than anxiety. Social concerns (fear of publicly observable symptoms of anxiety) were associated with both anxiety and depression in adolescence. Genetic influences on mental and social concerns were shared to a similar extent with both anxiety and depression.

Conclusions. Phenotypic patterns of cognitive specificity and broader genetic associations between anxiety sensitivity dimensions, anxiety and depressive disorder symptoms were similar at all waves. Both disorder-specific and shared cognitive concerns were identified, suggesting it is appropriate to classify anxiety and depression as distinct but related disorders and confirming the clinical perspective that cognitive therapy is most likely to benefit by targeting cognitive concerns relating specifically to the individual's presenting symptoms across development.

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Key words: Anxiety, anxiety sensitivity dimensions, cognitive specificity, depression, development, genetics, twins.

Introduction

Anxiety and depressive disorders are common and frequently co-morbid (Axelson & Birmaher, 2001). The distinctiveness of anxiety and depression is the subject of ongoing nosological debate concerning their classification in the updated psychiatric diagnostic manual, DSM-5 (Andrews *et al.* 2008). Some researchers question the utility of considering anxiety and depressive disorders as distinct clinical categories, given the considerable similarities in their presentation, aetiology and treatment (Axelson & Birmaher, 2001). However, there are important distinctions. Anxiety and depressive disorders can occur in isolation, twin studies reveal that whereas genetic influences are largely shared, environmental influences are generally distinct (Kendler *et al.* 1987) and preliminary neuroimaging studies show differential neural correlates (Phan *et al.* 2002; Vytal & Hamann, 2010).

The classification of anxiety and depression also has important clinical implications. If anxiety and depression are considered a single disorder then a unified treatment should be recommended, whereas discrete disorders suggest distinct interventions are required. Cognitive behavioural therapy (CBT) is a leading treatment for both anxiety and depression globally and is recommended as the first-line treatment in the USA (AACAP, 2007) and the UK (NICE, 2011). The premise of CBT is the modification of maladaptive cognitions maintaining emotional symptoms. The

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cognitive content specificity (CCS) hypothesis proposes that, although anxious and depressed individuals both have distorted cognitions, the content differs across these disorders (Beck & Perkins, 2001). Specifically, it is hypothesized that depressed individuals tend to think negatively about the self and focus on experiences of loss whereas anxious individuals focus on perceived threat or danger. In line with this model, the cognitive concerns targeted in CBT tend to vary across anxiety and depressive disorders (Brewin, 1996).

Given the implications of the CCS hypothesis for classifying and treating anxiety and depressive disorders, cognitive distortions associated with anxiety and depression need to be studied together to investigate the extent to which they are specific to each disorder or shared between them. Little is known about the role of shared and specific cognitions in the development of anxiety and depressive disorders in young people.

Anxiety sensitivity: associations with anxiety and depression

Anxiety sensitivity is of particular interest when considering common and specific cognitive content in anxiety and depression. Anxiety sensitivity refers to an enhanced sensitivity towards symptoms of anxiety such as heart palpitations or worry, with a belief that these are harmful (Taylor, 1999). The distinct nature of anxiety sensitivity compared to trait anxiety has been well established, in relation to both self-reported symptoms and laboratory-induced anxiety responses (McNally & Rapee, 1996; Rabian *et al.* 1999). Anxiety sensitivity also predicts future anxiety symptoms above and beyond concurrent anxious symptoms (Weems *et al.* 1998; McLaughlin *et al.* 2007; Waszczuk *et al.* 2013). Of note, despite its initial conceptualization as a risk factor for panic disorder (Reiss & McNally, 1985), anxiety sensitivity has been found to be associated with a wide range of anxiety symptoms and disorders and with depression (Weems *et al.* 1997; Naragon-Gainey, 2010; Waszczuk *et al.* 2013).

One possible reason for this wide range of associations is that anxiety sensitivity measures include multiple subscales (e.g. physical, mental and social concerns) that may be differentially associated with anxiety and depression.

Anxiety sensitivity: subscale analyses

Early investigations of anxiety sensitivity found that the physical concerns dimension (fear of biological symptoms; e.g. 'When my stomach hurts, I worry that I might be really sick') was more frequently associated with anxiety than depression (Joiner *et al.* 2002; Muris, 2002). The relationship of physical concerns with anxiety remained significant after controlling for co-occurring depression symptoms (Taylor *et al.* 1996; Schmidt *et al.* 1998; Dehon *et al.* 2005). Conversely, the mental concerns subscale, which depicts worries regarding cognitive control over anxiety symptoms (e.g. 'When I am afraid, I worry I might be going crazy'), is more frequently associated with depression (Muris, 2002), although other studies report associations with both anxiety and depression (Taylor *et al.* 1996; Schmidt *et al.* 1998; Dehon *et al.* 2005) or with anxiety but not depression (Joiner *et al.* 2002). The social concerns subscale, reflecting fears of publicly observable symptoms of anxiety (e.g. 'I don't like to let my feelings show'), seems to be associated with both anxiety and depression (Dehon *et al.* 2005), although others show stronger association with anxiety symptoms (Taylor *et al.* 1996; Schmidt *et al.* 1998). Although there is debate regarding the specific number and content of anxiety sensitivity subscales, confirmatory factor analytic studies (Wright *et al.* 2010) and a twin study by our group (Brown *et al.* 2012) support a hierarchical structure of anxiety sensitivity with three dimensions representing physical, social and mental concerns.

Mixed results across studies, particularly for mental and social concerns dimensions, could represent developmental differences in associations between anxiety sensitivity dimensions, anxiety and depression. However, a study of global anxiety sensitivity from our team found consistent associations with anxiety and depression symptoms across multiple time points in adolescence (Zavos *et al.* 2012*b*). Additionally, as multiple age groups are rarely included in single studies, particularly examining associations with anxiety sensitivity dimensions, mixed results could simply reflect differences in sample characteristics (e.g. clinical *versus* non-clinical groups) and methodologies (e.g. derivation of anxiety sensitivity dimensions) across studies.

Anxiety sensitivity: genetic and environmental influences

Examining genetic and environmental associations between cognitive content, anxiety and depression can help to disentangle common and specific influences on these problems. Our team has previously shown a large genetic overlap between anxiety sensitivity and anxiety symptoms (0.89) in childhood (Waszczuk *et al.* 2013) and with both anxiety (0.86–0.87) and depression symptoms (0.70–0.76) in adolescence (Zavos *et al.* 2010). This is in line with the generalist genes hypothesis (Eley, 1997), which proposes that psychiatric traits that co-vary have similar genetic influences that account for their co-morbidity whereas non-shared

environmental influences are largely trait specific. However, to date, there are no studies examining aetiological influences on associations between specific anxiety sensitivity dimensions, anxiety and depression in any age range.

The current study

The current study examined cross-sectional, phenotypic and aetiological associations between anxiety sensitivity dimensions, anxiety and depressive disorder symptoms at five waves of data collection within three different stages in development: childhood, adolescence and early adulthood. To our knowledge this is the first study to take a developmental perspective and combine both phenotypic and genetically sensitive data to address this question. This allows us not only to explore the CCS hypothesis at different ages but also to identify whether associations are mirrored at the aetiological level.

Several hypotheses were generated. First, the physical concerns dimension of anxiety sensitivity was expected to be more strongly associated with anxiety than depressive disorder symptoms whereas mental concerns would be more strongly associated with depression than anxiety, and social concerns would be associated with both anxiety and depression to a similar extent. Second, we anticipated that these relationships would generally be consistent at the different data collection waves within childhood, adolescence and adulthood, in line with limited multiple time-point studies of global anxiety sensitivity. Third, in line with the generalist genes hypothesis, we hypothesized that genetic associations would mirror the pattern of phenotypic associations. We expected stronger genetic correlations between physical concerns and anxiety and between mental concerns and depression, with social concerns showing a similar genetic overlap with both anxiety and depressive disorders symptoms.

Method

Participants

The present analyses combined data from two longitudinal twin and sibling datasets: the Emotions, Cognitions, Heredity and Outcome (ECHO) and Genesis G12-19 (G1219) studies. ECHO is a spin-off of a larger population sample with most of the twin pairs being selected for heightened parent-report anxiety at 7 years. G1219 is an unselected twin and sibling study. Full recruitment details are provided elsewhere (Eley *et al.* 2007; McAdams *et al.* 2013). Both studies were approved by the appropriate ethics committees (Research Ethics Committee, Institute of Psychiatry, King's College London and Goldsmiths, University of London). Informed consent was obtained from parents of all children aged under 16 years and from participants over 16 themselves. Zygosity was determined using parent-rated questionnaires (Cohen *et al.* 1975; Price *et al.* 2000) and DNA sequencing in uncertain cases. The current report focuses on five waves of data collected during childhood, adolescence and adulthood: wave 1 (mean age=8 years) and wave 2 (mean age=10) from ECHO, and waves 3 (mean age=15), 4 (mean age=17) and 5 (mean age=20) from G1219. Sample characteristics are shown in Table 1. There were wide age ranges for waves 3–5, reflecting the inclusion of siblings in G1219. However, the majority of the sample at each wave conferred much narrower age ranges (e.g. >90% 18–22 years at wave 5)[1]†.

Measures

Anxiety sensitivity

Anxiety sensitivity was assessed using the Children's Anxiety Sensitivity Index (CASI; Silverman *et al.* 1991) at waves 1–4 and the Anxiety Sensitivity Index (ASI; Reiss *et al.* 1986) at wave 5. Both involve participants completing items reflecting fear of anxiety sensations and have sound psychometric properties. Anxiety sensitivity dimensions representing physical, social and mental concerns were defined based on previous factor analyses in the G1219 study (Brown *et al.* 2012). Physical concerns consisted of 12 items assessing worries regarding physical symptoms of anxiety. Social and mental concerns dimensions each contained three items relating to publicly observable symptoms of anxiety and worries about cognitive control respectively. At wave 5, physical and social concerns dimensions had 11 and two items respectively because the ASI had fewer overall items than the CASI. Dimension scores were calculated by summing constituent items for each subscale.

Anxiety

DSM-based anxiety symptoms were assessed using the Screen for Child Anxiety Related Emotional Disorders (SCARED; Birmaher *et al.* 1999) at waves 1 and 2 (mean ages 8 and 10) and the Spence Children's Anxiety Scale (SCAS; Spence, 1998) at waves 3 and 4 (mean ages 15 and 17). At wave 5 (mean age 20), an adult variant (Gregory *et al.* 2011) of the anxiety items from the Revised Children's Anxiety and Depression Scales (RCADS; Chorpita *et al.* 2000) was used. All measures represent self-report questionnaires tapping common anxiety symptoms and show sound psychometric

† The notes appear after the main text.

Table 1. *Sample characteristics and descriptive statistics for anxiety sensitivity dimensions, anxiety and depressive disorder symptoms in childhood, adolescence and adulthood*

	Wave 1 (ECHO)	Wave 2 (ECHO)	Wave 3 (G1219)	Wave 4 (G1219)	Wave 5 (G1219)
n (pairs)	300	250	1,372	866	896
Female/Male, *n* (%)	169.5 (57)/130.5(43)	141(56)/109(44)	768(56)/604(44)	520(60)/346(40)	547(61)/349(39)
Age (years.months), mean (range)	8.6 (8.2–8.11)	10.1 (9.7–10.10)	15.0 (12.0–21.0)	17.0 (14.0–23.0)	20.0 (18.0–27.0)
Zygosity (MZ/DZS/DZO/Sib)	100/82/117/0	83/69/98/0	350/313/334/330[a]	234/207/232/182[a]	230/214/232/201[a]
Anxiety sensitivity	31.31 (6.24)	30.32 (5.51)	28.73 (5.55)	25.65 (5.72)	31.52 (9.41)
Physical	21.01 (4.80)	20.22 (4.37)	18.61 (4.32)	16.14 (4.17)	20.47 (7.37)
Social	5.98 1.47)	6.19 (1.20)	6.32 (1.43)	5.92 (1.69)	6.58 (1.85)
Mental	4.33 (1.47)	3.91 (1.17)	3.80 (1.14)	3.60 (1.07)	4.48 (2.10)
Anxiety	29.39 (12.63)	25.17 (11.59)	28.85 (13.66)	20.62 (12.80)	25.06 (14.88)
Depression	10.27 (6.94)	8.22 (5.82)	8.08 (6.65)	6.25 (5.33)	6.45 (5.73)

ECHO, Emotions, Cognitions, Heredity and Outcome; MZ, monozygotic; DZS, dizygotic, same-sex pairs; DZO, dizygotic, opposite-sex pairs; Sib, siblings.

[a] The numbers of twin pairs do not add up to totals because some of the twins were of unknown zygosity (wave 3=45, wave 4=11, wave 5=19). These pairs were excluded from the genetic analyses.

Summary statistics are presented on untransformed and unregressed variables for comparison with other published samples.

Different measures of anxiety sensitivity, anxiety and depression were used at different waves, thus the means cannot be compared across some waves.

The wider age ranges at waves 3–5 reflect the inclusion of siblings. The majority of the sample at each time point confer much narrower age ranges (e.g. >90% 18–22 at wave 5).

properties. Responses were summed across items on each measure to create total anxiety scores.

All analyses at waves 1 and 2 were repeated removing one item from the SCARED that overlapped with the CASI: 'When I get frightened, I feel like I am going crazy'. However, the results did not differ meaningfully so analyses with full measures are reported here.

Depression

DSM-based depressive disorder symptoms were assessed using the Children's Depression Inventory (CDI; Kovacs, 1985) in ECHO (waves 1 and 2) and the Short Mood and Feelings Questionnaire (SMFQ; Angold *et al.* 1995) in G1219 (waves 3–5). Both self-report measures demonstrate sound psychometric properties. Total depression scores were created by summing response across all items.

Analyses

Phenotypic analyses

Phenotypic associations between anxiety sensitivity dimensions, anxiety and depression were examined at each wave using full correlations. Owing to substantial covariance between anxiety sensitivity dimensions and co-occurrence of anxiety and depressive disorders symptoms, partial correlations were used at each wave to tease apart phenotypic specificity. Pair-wise partial correlations controlled for associations with other variables (e.g. associations between physical concerns and anxiety controlled for the other anxiety sensitivity dimensions and depression).

Genotypic analyses

Aetiological associations between anxiety sensitivity dimensions, anxiety and depressive disorders symptoms were examined at each wave using structural equation twin modelling. By comparing the degree of similarity of monozygotic (MZ) twins (sharing all of their segregating genes) to dizygotic (DZ) twins (sharing half of their segregating genes on average), the twin design decomposes the variance within a variable into additive genetic influences (A), common environmental influences that make family members more alike (C) and non-shared, individual-specific environmental influences (E). The genetic and environmental overlap between multiple measures can be examined by comparing the MZ:DZ ratio of cross-twin, cross-trait covariances.

Prior to twin analyses, all variables were regressed for the effects of age and sex to meet twin modelling assumptions and mapped onto a standard normal distribution using the rank-based van der Waerden

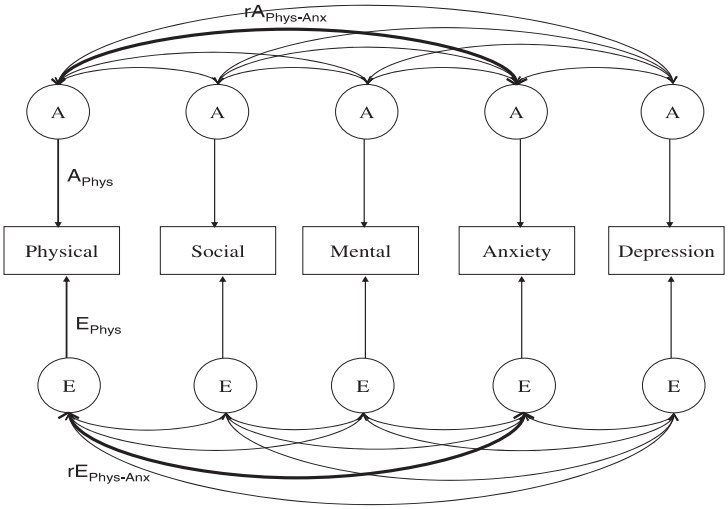

Fig. 1. Correlated factors solution showing genetic and environmental associations between anxiety sensitivity subscales (physical, social and mental concerns) and anxiety and depressive disorder symptoms. Phys, Physical concerns; A, additive genetic; E, non-shared environment; *r*A, genetic correlation; *r*E, non-shared environmental correlation. Paths in bold are highlighted and labelled for descriptive purposes only. For example, the path labelled A_{Phys} represents the genetic effects on the physical concerns dimension of anxiety sensitivity and the path labelled $rA_{Phys\text{-}Anx}$ depicts the degree to which genetic influences on the physical concerns dimensions of anxiety sensitivity are correlated with genetic effects on anxiety symptoms. Similarly, $rE_{Phys\text{-}Anx}$ represents the degree to which non-shared environmental factors influencing physical concerns are correlated with those influencing anxiety symptoms. Shared environmental estimates (C) and correlations (*r*C) were also calculated. However, these were non-significant so for simplicity are not shown in the figure. Estimates for C and *r*C are reported in Tables S1 and S3 respectively.

transformation to correct for skew. Twin models were fitted using the OpenMx program (Boker *et al.* 2011) in R (RDC Team, 2010), a structural equation modelling package for the analysis of genetically informative data that controls for the non-independence of family members. Sampling weights were incorporated in ECHO twin models to account for the selected nature of the sample (Lau *et al.* 2007). Model fit to a saturated model was assessed for both univariate and multivariate models at each wave using minus twice the log likelihood (−2LL) of the observations and the Akaike information criterion (AIC). Univariate analyses assessing the influences of A, C and E on all variables were conducted at each wave. Sex differences were examined to inform multivariate modelling. Because of the sample size, sex differences were only examined in the G1912 sample to inform twin modelling. Scalar (i.e. variance) sex differences were found for all variables except for social concerns. Therefore, variance differences were included in the model-fitting analyses.

Multivariate correlated factors solutions examined the genetic and environmental relationships between anxiety sensitivity dimensions, anxiety and depression at each wave. The correlated factor solution (Fig. 1) assumes that each variable has unique genetic and environmental influences (e.g. A_{Phys}, C_{Phys}, E_{Phys}) but that these are correlated with one another (e.g. $rA_{Phys\text{-}Anx}$, $rC_{Phys\text{-}Anx}$ and $rE_{Phys\text{-}Anx}$ respectively for genetic, shared environment and non-shared environment correlations between physical concerns and anxiety). Thus, the curved arrow from the A term above the physical anxiety sensitivity subscale to the A term above the anxiety scale represents the genetic correlation between these two variables.

The relative strength of genetic and non-shared environmental estimates for each variable and for correlations between variables was compared using likelihood-based confidence intervals (CIs). Non-overlapping CIs indicate significant differences.

Finally, the focus of the current results was on associations between different anxiety sensitivity subscales and anxiety and depressive symptoms. Phenotypic and genetic associations among anxiety sensitivity subscales, and also between anxiety and

depression, are presented elsewhere (Zavos *et al.* 2010; Brown *et al.* 2012).

Ethical standards

All procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Results

Descriptive statistics

Descriptive statistics of all measures are presented in Table 1. Descriptive statistics results are reported on raw untransformed data to facilitate comparisons with other studies. The majority of variables demonstrated substantial internal consistency at all waves (α=0.79–0.94 for anxiety and depression; α=0.25–0.86 for anxiety sensitivity subscales). Estimates were somewhat lower for social and mental concerns dimensions because there were fewer items within those subscales. However, estimates were comparable to other samples (Walsh *et al.* 2004; Joiner *et al.* 2002).

Phenotypic results

Full and partial Pearson correlations are presented in Table 2. For the physical concerns dimensions of anxiety sensitivity, full correlations indicated significantly stronger associations with anxiety than depressive disorder symptoms at all waves ($r_{\text{Phys-Anx}}$=0.52–0.71, $r_{\text{Phys-Dep}}$=0.25–0.51). This was confirmed by partial correlations. The association between physical concerns and anxiety remained significant whereas partial correlations with depression became non-significant and near-zero at most waves.

Social concerns were associated with both anxiety and depression to a similar extent at all ages ($r_{\text{Soc-Anx}}$=0.20–0.40, $r_{\text{Soc-Dep}}$=0.05–0.43), although associations with depression were weaker at waves 1 and 2 (mean ages 8 and 10 respectively). Partial correlations revealed no association between social concerns and either anxiety or depression at waves 1, 2 and 5 but significantly stronger associations with depression than anxiety at the time points covering adolescence (waves 3 and 4).

Finally, full correlations for mental concerns revealed similar associations with anxiety and depressive disorder symptoms at all waves ($r_{\text{Ment-Anx}}$=0.36–0.60, $r_{\text{Ment-Dep}}$=0.28–0.54). Partial correlations showed a tendency for stronger associations with depression than anxiety, which reached significance at wave 4 [0.28 (95% CI 0.22–0.34) and 0.10 (95% CI 0.03–0.17) for depression and anxiety respectively].

Genetic associations

Univariate estimates

Univariate genetic and environmental estimates indicated small to moderate genetic effects (0.12–0.46), small but non-significant shared environmental influences (0.00–0.12) and large non-shared environmental influences (0.49–0.84) on all variables (see online Supplementary Table S1). Depression at wave 2 was an exception, being influenced by moderate shared environmental factors with no genetic influence (see note to Table S1 for further details).

Multivariate estimates

Genetic and non-shared environmental correlations between the variables at each wave are shown in Table 3 (fit statistics in Supplementary Table S2). Because of small non-significant shared environmental estimates on all variables, shared environmental correlations were modelled but were non-significant and thus are not interpreted further (see Supplementary Table S3).

Genetic correlations between the physical concerns dimensions of anxiety sensitivity and anxiety and depression are given in the first column of Table 3. Physical concerns showed substantial genetic overlap with anxiety symptoms at all ages ($r\text{A}_{\text{Phys-Anx}}$=0.78–0.96) whereas genetic correlations between physical concerns and depression symptoms were weaker at all time points ($r\text{A}_{\text{Phys-Dep}}$=0.15–0.87). Non-shared environmental correlations for physical concerns were also stronger for anxiety than depression ($r\text{E}_{\text{Phys-Anx}}$= 0.44–0.55, $r\text{E}_{\text{Phys-Dep}}$=0.18–0.39). These latter differences were significant at waves 3 and 5 [e.g. $r\text{E}_{\text{Phys-Anx}}$=0.51 (95% CI 0.45–0.58), $r\text{E}_{\text{Phys-Dep}}$ 0.24 (95% CI 0.15–0.32) at wave 3, mean age 15 years].

Social concerns had moderate to large genetic correlations with both anxiety and depression at all time points ($r\text{A}_{\text{Soc-Anx}}$=0.32–0.74, $r\text{A}_{\text{Soc-Dep}}$=0.43–0.71). Non-shared environmental correlations with anxiety and depression were comparable at all time points ($r\text{E}_{\text{Soc-Anx}}$=0.12–0.39, $r\text{E}_{\text{Soc-Dep}}$=0.19–0.41). Similarly, mental concerns generally showed moderate to large genetic ($r\text{A}_{\text{Ment-Anx}}$=0.46–0.86, $r\text{A}_{\text{Ment-Dep}}$=0.04–0.71) and modest to moderate non-shared environmental correlations ($r\text{E}_{\text{Ment-Anx}}$=0.21–0.41, $r\text{E}_{\text{Ment-Dep}}$=0.19–0.41) with both anxiety and depression at all waves. An exception was the lack of genetic correlation between mental concerns and depression at wave 2 (see footnote to Table S1).

Table 2. *Full and partial correlations between anxiety sensitivity dimensions and anxiety and depression across childhood, adolescence and early adulthood*

		Full correlations			Partial correlations		
		Anxiety sensitivity dimensions			Anxiety sensitivity dimensions		
		Physical	Social	Mental	Physical	Social	Mental
Wave 1. Child (mean age 8)	Anxiety	**0.52** (0.43 to 0.60)	**0.20** (0.09 to 0.31)	**0.42** (0.32 to 0.51)	**0.34** (0.24 to 0.44)	0.09 (to 0.02 to 0.20)	**0.17** (0.06 to 0.28)
	Depression	**0.26** (0.15 to 0.36)	0.05 (−0.06 to 0.16)	**0.30** (0.19 to 0.40)	0.02 (−0.09 to 0.13)	−0.04 (−0.15 to 0.07)	**0.14** (0.03 to 0.25)
Wave 2. Child (mean age 10)	Anxiety	**0.64** (0.56 to 0.71)	**0.26** (0.14 to 0.37)	**0.36** (0.25 to 0.46)	**0.53** (0.44 to 0.61)	0.07 (−0.05 to 0.19)	0.04 (−0.08 to 0.16)
	Depression	**0.25** (0.09 to 0.33)	**0.15** (0.03 to 0.27)	**0.28** (0.16 to 0.39)	−0.01 (−0.14 to 0.11)	0.07 (−0.05 to 0.19)	**0.18** (0.06 to 0.30)
Wave 3. Adolescent (mean age 15)	Anxiety	**0.67** (0.64 to 0.70)	**0.28** (0.23 to 0.33)	**0.47** (0.43 to 0.51)	**0.51** (0.47 to 0.53)	0.03 (to 0.02 to 0.08)	**0.15** (0.10 to 0.20)
	Depression	**0.43** (0.39 to 0.47)	**0.29** (0.24 to 0.34)	**0.42** (0.38 to 0.46)	−0.01 (−0.06 to 0.04)	**0.14** (0.09 to 0.19)	**0.20** (0.15 to 0.25)
Wave 4. Adolescent (mean age 17)	Anxiety	**0.71** (0.68 to 0.74)	**0.40** (0.34 to 0.45)	**0.48** (0.42 to 0.53)	**0.55** (0.50 to 0.59)	0.06 (0.00 to 0.13)	**0.10** (0.03 to 0.17)
	Depression	**0.51** (0.46 to 0.56)	**0.43** (0.38 to 0.48)	**0.54** (0.49 to 0.59)	**0.08** (0.01 to 0.15)	**0.22** (0.16 to 0.28)	**0.28** (0.22 to 0.34)
Wave 5. Adult (mean age 20)	Anxiety	**0.69** (0.66 to 0.72)	**0.26** (0.20 to 0.32)	**0.60** (0.56 to 0.64)	**0.45** (0.40 to 0.50)	0.05 (to 0.02 to 0.12)	**0.23** (0.17 to 0.29)
	Depression	**0.42** (0.37 to 0.47)	**0.19** (0.13 to 0.25)	**0.50** (0.45 to 0.55)	−0.03 (−0.10 to 0.04)	0.03 (−0.04 to 0.10)	**0.15** (0.09 to 0.21)

95% Confidence intervals (CIs) are presented in parentheses. CIs not inclusive of zeros indicate significant correlations (in bold). Non-overlapping CIs mean significant difference between the values. Partial correlations controlled for all other variables within time (e.g. anxiety with physical concerns controlling for covariance with depression and social and mental concerns).

Results are presented for untransformed and unregressed variables for comparison with other published samples. Correlations were conducted on a random selection of one twin from each twin pair to ensure that the relatedness between pairs within the sample did not influence the associations between variables.

Table 3. *Genetic and non-shared environmental correlations between anxiety sensitivity dimensions and anxiety and depression across childhood, adolescence and early adulthood*

		Genetic			Non-shared environment		
		Anxiety sensitivity dimensions			Anxiety sensitivity dimensions		
		Physical	Social	Mental	Physical	Social	Mental
Wave 1. Child (mean age 8)	Anxiety	0.95 (0.45 to 1.00)	0.46 (−1.00 to 1.00)	0.86 (0.45 to 1.00)	0.44 (0.32 to 0.56)	0.22 (0.08 to 0.37)	0.23 (0.09 to 0.37)
	Depression	0.15 (−0.78 to 0.81)	0.43 (−1.00 to 1.00)	0.48 (−0.28 to 1.00)	0.24 (0.08 to 0.39)	0.09 (−0.06 to 0.24)	0.19 (0.03 to 0.34)
Wave 2. Child (mean age 10)	Anxiety	0.96 (−1.00 to 1.00)	0.32 (−1.00 to 1.00)	0.56 (−1.00 to 1.00)	0.52 (0.39 to 0.62)	0.17 (0.00 to 0.34)	0.21 (0.04 to 0.38)
	Depression	0.87 (−1.00 to 1.00)	0.54 (−1.00 to 1.00)	0.04 (−1.00 to 1.00)	0.18 (0.02 to 0.35)	0.04 (−0.12 to 0.21)	0.27 (0.10 to 0.43)
Wave 3. Adolescent (mean age 15)	Anxiety	0.78 (0.61 to 0.87)	0.57 (0.33 to 1.00)	0.59 (0.37 to 0.81)	0.51 (0.45 to 0.58)	0.22 (0.13 to 0.29)	0.28 (0.20 to 0.37)
	Depression	0.59 (0.33 to 0.90)	0.67 (0.31 to 1.00)	0.54 (0.23 to 0.84)	0.24 (0.15 to 0.32)	0.15 (0.07 to 0.24)	0.28 (0.19 to 0.37)
Wave 4. Adolescent (mean age 17)	Anxiety	0.92 (0.69 to 1.00)	0.46 (0.11 to 0.88)	0.46 (0.05 to 0.75)	0.54 (0.46 to 0.61)	0.39 (0.29 to 0.48)	0.40 (0.29 to 0.49)
	Depression	0.58 (0.41 to 0.93)	0.59 (0.17 to 0.93)	0.56 (0.09 to 0.83)	0.39 (0.29 to 0.48)	0.31 (0.21 to 0.41)	0.41 (0.30 to 0.50)
Wave 5. Adult (mean age 20)	Anxiety	0.90 (0.67 to 1.00)	0.74 (0.43 to 1.00)	0.83 (0.56 to 1.00)	0.55 (0.47 to 0.63)	0.12 (0.01 to 0.23)	0.41 (0.31 to 0.51)
	Depression	0.69 (0.29 to 1.00)	0.71 (0.37 to 1.00)	0.71 (0.39 to 0.99)	0.30 (0.19 to 0.40)	0.29 (0.01 to 0.19)	0.32 (0.22 to 0.43)

95% Confidence intervals (CIs) are presented in parentheses. CIs not inclusive of zeros indicate significant correlations. Non-overlapping CIs mean significant difference between the values.

Because of small non-significant shared environmental estimates on all variables, shared environmental correlations could not be reliably estimated. These are reported in the supplementary material (see Table S4) for the interested reader but cannot be meaningfully interpreted.

Discussion

The current study reports cross-sectional analyses of shared and specific cognitive distortions in anxiety and depression at different development stages. This is the first study to investigate both phenotypic and genetic associations between anxiety sensitivity dimensions and anxiety and depressive disorder symptoms and to examine cross-sectional associations at five waves during childhood, adolescence and adulthood.

Partial correlations showed that the physical concerns dimension of anxiety sensitivity was associated with anxiety but not depression and shared greater genetic influences with anxiety than depression at all waves. Mental concerns were independently related to both anxiety and depression symptoms across development, with a tendency for stronger associations with depression than anxiety. Social concerns were not specifically associated with anxiety or depression in childhood and adulthood but tended to have stronger associations with depression than anxiety symptoms in adolescence. Genetic and non-shared environmental influences on mental and social concerns were moderately correlated with both anxiety and depression symptoms at all waves, although genetic correlations tended to be higher than non-shared environmental correlations. The results were similar at the three developmental periods, suggesting continuity over time in the patterns of associations between anxiety sensitivity dimensions and anxiety and depressive disorder symptoms. However, longitudinal research is needed to explore stability in the relationships between anxiety sensitivity dimensions, anxiety and depression.

Phenotypic results were largely in agreement with previous studies, finding stronger associations between physical concerns and anxiety, and between mental concerns and depression (Muris, 2002). However, they are in contrast to those suggesting that anxiety sensitivity is primarily associated with anxiety, and that associations with depression are driven by the co-occurrence between depression and anxiety (Joiner *et al.* 2002). Differential associations between anxiety sensitivity dimensions, anxiety and depression partially supported the CCS hypothesis, that anxiety and depression can be differentiated by divergent cognitive themes (Beck & Perkins, 2001), and support a multifaceted model of anxiety sensitivity, consisting of distinct but related dimensions that play different roles in anxiety and depression. Future research should use anxiety sensitivity subscale scores, in addition to global scores, to clarify the broad associations identified between anxiety sensitivity and a range of anxiety and depressive disorders.

Our genetic results were largely in line with previous twin studies exploring aetiological associations between global anxiety sensitivity and anxiety and depression (Zavos *et al.* 2010). Moderate to substantial genetic overlap and modest non-shared environmental correlations between anxiety sensitivity dimensions and anxiety and depression symptoms are in accordance with the generalist genes hypothesis (Eley, 1997), highlighting that similarities between these constructs are driven by genetic rather than environmental factors. Furthermore, broad genetic associations are in line with high rates of co-occurrence between anxiety and depression (Seligman & Ollendick, 1998) and between cognitive risk factors for both sets of symptoms (Zavos *et al.* 2010). Evidence for shared genetic effects has implications for molecular genetic studies, supporting the persuasive argument that including cases with anxiety and depression disorders would lead to increasing power to detect shared susceptibility loci (Hettema, 2008).

Conversely, evidence for phenotypic specificity in associations between anxiety sensitivity, anxiety and depression and unique environmental influences acting on these symptoms has clinical implications for therapeutic interventions. Identifying disorder-specific cognitive concerns, and also those shared between co-morbid disorders such as anxiety and depression, could continue to inform the tailoring of CBT programmes to a given diagnosis. For example, the physical concerns dimension of anxiety sensitivity relates to fear of biological symptoms of distress. These symptoms are central to anxiety but not so typical of depression, which is characterized more by sadness than fear. Conversely, mental and social concerns showed independent associations with both anxiety and depression, especially at later waves, suggesting there may be shared cognitive concerns in both sets of symptoms; for example, fear of losing mental control is captured in the mental concerns subscale and symptoms regarding control and distractibility are common in both anxiety and depressive disorders.

Associations between all anxiety sensitivity dimensions and anxiety suggest general modifications of anxiety-related cognitive concerns may be useful in CBT for anxiety disorders. However, anxiety represents a heterogeneous phenotype. Although beyond the scope of the current paper, future research would benefit from exploring specificity of associations between anxiety sensitivity dimensions and a range of anxiety disorder symptoms, independent of depression symptoms, to tailor cognitive interventions more precisely to specific anxiety disorders.

Associations between depression symptoms and mental and social concerns but not physical concerns dimensions of anxiety sensitivity are in line with current practice in CBT for depressive disorders, which focuses on modifying concerns surrounding

cognitive and social symptoms rather than physical symptoms. Importantly, stronger associations in adolescence than in childhood and adulthood suggest that targeting social concerns may be most useful in adolescent depression. This developmental difference may be attributable to the fact that depression tends to emerge later than anxiety (Cohen *et al.* 1993) and fits with normal developmental trajectories of fears, which suggest that fears relating to social themes emerge later in young people than those relating to biological symptoms (Gullone, 2000). However, depression-specific research has implicated several other cognitive distortions in the development of depressive symptoms (Nolen-Hoeksema *et al.* 2008). Future research should aim to explore the content of depressive cognitions in more detail by combining multiple cognitive distortions within a single study.

Limitations

The genetically informative samples and multiple points are considerable strengths of the current study. However, the limitations of the study warrant consideration.

First, to ensure that age-appropriate inventories were used, measures differed across some waves. However, as all selected measures have previously been validated in similar samples and current analyses were not longitudinal, this should not limit the interpretation of our results (for longitudinal analyses of anxiety sensitivity, anxiety and depression, see Zavos *et al.* 2012*a*). Second, the extent to which young children can understand and report on internalizing symptoms is debated (Chorpita *et al.* 1996). Nevertheless, children as young as age 8 can make valid reports of internalizing symptoms (Michael & Merrell, 1998; Merrell *et al.* 2002) and interpretations of anxiety symptoms (Muris *et al.* 2004). Given the internal replication of the results at all waves, in two different samples, our findings seem broadly applicable across development. Nonetheless, reliance on self-report data may be associated with shared method variance that could inflate the correlations. Third, measurement of anxiety sensitivity dimensions was limited by social and mental concerns dimensions containing only three items, resulting in lower internal consistency. However, the ASI and CASI are the only currently available self-report measures of anxiety sensitivity. Given the considerable evidence for a multifaceted construct, expanding measures of anxiety sensitivity to better capture social and mental concerns would be beneficial. Fourth, overlapping age ranges for waves 3 to 5 because of the inclusion of siblings could be argued to limit our ability to draw conclusions about patterns of associations across development. However, the majority of the sample fell within more discrete, non-overlapping age ranges at each wave, and when analyses were run without siblings the findings were very similar. We retained the siblings in our final models as their inclusion enhances the generalizability of our findings to non-twin populations.

With regard to twin analyses, the child sample was somewhat smaller than the adolescent/adult sample. Although considered large for phenotypic analyses, the paediatric sample had reduced power to detect shared environmental influences and parameter estimates resulted in larger CIs. It will be important to replicate the current results in larger paediatric twin studies. Additionally, there are some limitations inherent to the twin design, comprehensively discussed elsewhere (Plomin *et al.* 2012). These limitations have minimal and contrasting effects but parameter estimates should be taken as indicative rather than absolute values.

Conclusions

The results of the current study support and extend previous research examining specificity in associations between anxiety sensitivity dimensions, anxiety and depression and add to our growing understanding of co-morbidity between anxiety and depressive disorder symptoms. Specifically, anxiety sensitivity is a multifaceted construct. Distinct dimensions of anxiety sensitivity are differentially associated with anxiety and depression, indicating that anxiety and depressive disorder symptoms are characterized by both shared and symptom-specific cognitive distortions. Hence, the results from the current study are in agreement with the current DSM-5 classification that conceptualizes depression and anxiety as two separate, yet highly co-morbid, disorders. Furthermore, identifying specific and shared cognitions in anxiety and depression can inform the design of more precise clinical interventions for anxiety and depressive disorders across development.

Note

[1] All analyses for waves 3–5 were repeated excluding the sibling pairs to examine whether their more varied ages affected the results. There were no significant differences in the point estimates or in the interpretation of any of the results.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291714000828.

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Declaration of Interest

None.

References

AACAP (2007). Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. *Journal of the American Academy of Child and Adolescent Psychiatry* **46**, 267–283.

Andrews G, Anderson T, Slade T, Sunderland M (2008). Classification of anxiety and depressive disorders: problems and solutions. *Depression and Anxiety* **25**, 274–281.

Angold A, Costello EJ, Messer SC, Pickles A, Winder F, Silver D (1995). The development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. *International Journal of Methods in Psychiatric Research* **5**, 1–12.

Axelson DA, Birmaher B (2001). Relation between anxiety and depressive disorders in childhood and adolescence. *Depression and Anxiety* **14**, 67–78.

Beck R, Perkins TS (2001). Cognitive content-specificity for anxiety and depression: a meta-analysis. *Cognitive Therapy and Research* **25**, 651–663.

Birmaher B, Brent DA, Chiappetta L, Bridge J, Monga S, Baugher M (1999). Psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED): a replication study. *Journal of the American Academy of Child and Adolescent Psychiatry* **38**, 1230–1236.

Boker S, Neale M, Maes H, Wilde M, Spiegel M, Brick T, Spies J, Estabrook R, Kenny S, Bates T (2011). OpenMx: an open source extended structural equation modeling framework. *Psychometrika* **76**, 306–317.

Brewin CR (1996). Theoretical foundations of cognitive-behavior therapy for anxiety and depression. *Annual Review of Psychology* **47**, 33–57.

Brown HM, Trzaskowski M, Zavos HMS, Rijsdijk FV, Gregory AM, Eley TC (2012). Phenotypic and genetic structure of anxiety sensitivity in adolescence and early adulthood. *Journal of Anxiety Disorders* **26**, 680–688.

Chorpita BF, Albano AM, Barlow DH (1996). Child Anxiety Sensitivity Index: considerations for children with anxiety disorders. *Journal of Clinical Child Psychology* **25**, 77–82.

Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE (2000). Assessment of symptoms of DSM-IV anxiety and depression in children: a revised child anxiety and depression scale. *Behaviour Research and Therapy* **38**, 835–855.

Cohen DJ, Dibble E, Grawe JM, Pollin W (1975). Reliably separating identical from fraternal twins. *Archives of General Psychiatry* **32**, 1371–1375.

Cohen P, Cohen J, Kasen S, Velez CN, Hartmark C, Johnson J, Rojas M, Brook J, Streuning EL (1993). An epidemiological study of disorders in late childhood and adolescence – I. Age- and gender-specific prevalence. *Journal of Child Psychology and Psychiatry* **34**, 851–867.

Dehon C, Weems CF, Stickle TR, Costa NM, Berman SL (2005). A cross-sectional evaluation of the factorial invariance of anxiety sensitivity in adolescents and young adults. *Behaviour Research and Therapy* **43**, 799–810.

Eley TC (1997). General genes: a new theme in developmental psychopathology. *Current Directions in Psychological Science* **6**, 90–95.

Eley TC, Gregory AM, Clark DM, Ehlers A (2007). Feeling anxious: a twin study of panic/somatic symptoms, anxiety sensitivity and heart-beat perception in children. *Journal of Child Psychology and Psychiatry* **48**, 1184–1191.

Gregory AM, Buysse DJ, Willis TA, Rijsdijk FV, Maughan B, Rowe R, Cartwright S, Barclay NL, Eley TC (2011). Associations between sleep quality and anxiety and depression symptoms in a sample of young adult twins and siblings. *Journal of Psychosomatic Research* **71**, 250–255.

Gullone E (2000). The development of normal fear: a century of research. *Clinical Psychology Review* **20**, 429–451.

Hettema J (2008). What is the genetic relationship between anxiety and depression? *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics* **148**, 140–146.

Joiner TE, Schmidt NB, Schmidt KL, Laurent J, Catanzaro SJ, Perez M, Pettit JW (2002). Anxiety sensitivity as a specific and unique marker of anxious symptoms in youth psychiatric inpatients. *Journal of Abnormal Child Psychology* **30**, 167–175.

Kendler KS, Heath AC, Martin NG, Eaves LJ (1987). Symptoms of anxiety and symptoms of depression. Same genes, different environments? *Archives of General Psychiatry* **44**, 451–457.

Kovacs M (1985). The Children's Depression Inventory (CDI). *Psychopharmacology Bulletin* **21**, 995–1124.

Lau J, Gregory A, Goldwin M, Pine D, Eley T (2007). Assessing gene-environment interactions on anxiety symptom subtypes across childhood and adolescence. *Development and Psychopathology* **19**, 1129–1146.

McAdams TA, Gregory AM, Rowe R, Zavos H, Barclay NL, Lau JY, Maughan B, Eley TC (2013). The Genesis 12—9 (G1219) Study: a twin and sibling study of gene-environment interplay and adolescent development in the UK. *Twin Research and Human Genetics* **16**, 134–143.

McLaughlin EN, Stewart SH, Taylor S (2007). Childhood Anxiety Sensitivity Index factors predict unique variance in DSM-IV anxiety disorder symptoms. *Cognitive Behaviour Therapy* **36**, 210–219.

McNally RJ, Rapee RM (1996). Anxiety sensitivity is distinguishable from trait anxiety. In *Current Controversies in the Anxiety Disorders* (ed. R. M. Rapee), pp. 214–227. Guilford Press: New York.

Merrell KW, McClun LA, Kempf KKG, Lund J (2002). Using self-report assessment to identify children with internalizing problems: validity of the internalizing symptoms scale for children. *Journal of Psychoeducational Assessment* **20**, 223–239.

Michael KD, Merrell KW (1998). Reliability of children's self-reported internalizing symptoms over short to medium-length time intervals. *Journal of the American Academy of Child and Adolescent Psychiatry* **37**, 194–201.

Muris P (2002). An expanded childhood anxiety sensitivity index: its factor structure, reliability, and validity in a non-clinical adolescent sample. *Behaviour Research and Therapy* **40**, 299–311.

Muris P, Hoeve I, Meesters C, Mayer B (2004). Children's perception and interpretation of anxiety-related physical symptoms. *Journal of Behavior Therapy and Experimental Psychiatry* **35**, 233–244.

Naragon-Gainey K (2010). Meta-analysis of the relations of anxiety sensitivity to the depressive and anxiety disorders. *Psychological Bulletin* **136**, 128–150.

NICE (2011). *CG113 Anxiety: NICE guidance* (guidance.nice.org.uk/CG113). London: National Institute for Health and Care Excellence.

Nolen-Hoeksema S, Wisco BE, Lyubomirsky S (2008). Rethinking rumination. *Perspectives on Psychological Science* **3**, 400–424.

Phan KL, Wager T, Taylor SF, Liberzon I (2002). Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *NeuroImage* **16**, 331–348.

Plomin R, DeFries JC, Knopik VS, Neiderhiser JM (2012). *Behavioral Genetics*. Worth Publishers: New York.

Price TS, Freeman B, Craig I, Petrill SA, Ebersole L, Plomin R (2000). Infant zygosity can be assigned by parental report questionnaire data. *Twin Research* **3**, 129–133.

Rabian B, Embry L, MacIntyre D (1999). Behavioral validation of the Childhood Anxiety Sensitivity Index in children. *Journal of Clinical Child Psychology* **28**, 105–112.

RDC Team (2010). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing: Vienna, Austria.

Reiss S, McNally R (1985). Expectancy model of fear. In *Theoretical Issues in Behavior Therapy* (ed. S. Reiss and R. R. Bootzin), pp. 107–122. Academic Press: New York.

Reiss S, Peterson R, Gursky D, McNally R (1986). Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. *Behaviour Research and Therapy* **24**, 1–8.

Schmidt NB, Lerew DR, Joiner TE (1998). Anxiety sensitivity and the pathogenesis of anxiety and depression: evidence for symptom specificity. *Behaviour Research and Therapy* **36**, 165–177.

Seligman LD, Ollendick TH (1998). Comorbidity of anxiety and depression in children and adolescents: an integrative review. *Clinical Child and Family Psychology Review* **1**, 125–144.

Silverman W, Fleisig W, Rabian B, Peterson R (1991). Childhood anxiety sensitivity index. *Journal of Clinical Child and Adolescent Psychology* **20**, 162–168.

Spence SH (1998). A measure of anxiety symptoms among children. *Behaviour Research and Therapy* **36**, 545–566.

Taylor S (1999). *Anxiety Sensitivity: Theory, Research and Treatment of the Fear of Anxiety*. Lawrence Erlbaum Associates: Mahwah, NJ.

Taylor S, Koch WJ, Woody S, McLean P (1996). Anxiety sensitivity and depression: how are they related? *Journal of Abnormal Psychology* **105**, 474–479.

Vytal K, Hamann S (2010). Neuroimaging support for discrete neural correlates of basic emotions: a voxel-based meta-analysis. *Journal of Cognitive Neuroscience* **22**, 2864–2885.

Walsh T, Stewart S, McLaughlin E, Comeau N (2004). Gender differences in Childhood Anxiety Sensitivity Index (CASI) dimensions. *Journal of Anxiety Disorders* **18**, 695–706.

Waszczuk MA, Zavos HMS, Eley TC (2013). Genetic and environmental influences on relationship between anxiety sensitivity and anxiety subscales in children. *Journal of Anxiety Disorders* **27**, 475–484.

Weems CF, Hammond-Laurence K, Silverman WK, Ferguson C (1997). The relation between anxiety sensitivity and depression in children and adolescents referred for anxiety. *Behaviour Research and Therapy* **35**, 961–966.

Weems CF, Hammond-Laurence K, Silverman WK, Ginsburg GS (1998). Testing the utility of the anxiety sensitivity construct in children and adolescents referred for anxiety disorders. *Journal of Clinical Child Psychology* **27**, 69–77.

Wright K, Asmundson G, McCreary D, Stewart S, McLaughlin E, Comeau M, Walsh T (2010). Confirmatory factor analysis of the childhood anxiety sensitivity index: a gender comparison. *Cognitive Behaviour Therapy* **39**, 225–235.

Zavos H, Rijsdijk F, Gregory A, Eley T (2010). Genetic influences on the cognitive biases associated with anxiety and depression symptoms in adolescents. *Journal of Affective Disorders* **124**, 45–53.

Zavos HM, Gregory AM, Eley TC (2012*a*). Longitudinal genetic analysis of anxiety sensitivity. *Developmental Psychology* **48**, 204–212.

Zavos HM, Rijsdijk FV, Eley TC (2012*b*). A longitudinal, genetically informative, study of associations between anxiety sensitivity, anxiety and depression. *Behavior Genetics* **42**, 592–602.

6. CHAPTER 6 - A MULTIVARIATE TWIN STUDY OF TRAIT MINDFULNESS, DEPRESSIVE SYMPTOMS AND ANXIETY SENSITIVITY

This chapter is presented as a published paper and is an exact copy of the following journal publication:

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Supplementary materials for this chapter are presented in **Appendix D**

DEPRESSION AND ANXIETY 32:254–261 (2015)

Research Article

A MULTIVARIATE TWIN STUDY OF TRAIT MINDFULNESS, DEPRESSIVE SYMPTOMS, AND ANXIETY SENSITIVITY

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Background: *Mindfulness-based therapies have been shown to be effective in treating depression and reducing cognitive biases. Anxiety sensitivity is one cognitive bias that may play a role in the association between mindfulness and depressive symptoms. It refers to an enhanced sensitivity toward symptoms of anxiety, with a belief that these are harmful. Currently, little is known about the mechanisms underpinning the association between mindfulness, depression, and anxiety sensitivity. The aim of this study was to examine the role of genetic and environmental factors in trait mindfulness, and its genetic and environmental overlap with depressive symptoms and anxiety sensitivity.* **Methods:** *Over 2,100 16-year-old twins from a population-based study rated their mindfulness, depressive symptoms, and anxiety sensitivity.* **Results:** *Twin modeling analyses revealed that mindfulness is 32% heritable and 66% due to nonshared environmental factors, with no significant influence of shared environment. Genetic influences explained over half of the moderate phenotypic associations between low mindfulness, depressive symptoms, and anxiety sensitivity. About two-thirds of genetic influences and almost all nonshared environmental influences on mindfulness were independent of depression and anxiety sensitivity.* **Conclusions:** *This is the first study to show that both genes and environment play an important role in the etiology of mindfulness in adolescence. Future research should identify the specific environmental factors that influence trait mindfulness during development to inform targeted treatment and resilience interventions. Shared genetic liability underpinning the co-occurrence of low mindfulness, depression, and anxiety sensitivity suggests that the biological pathways shared between these traits should also be examined. Depression and Anxiety 32:254–261, 2015.* ©

Key words: *mindfulness; depression; anxiety sensitivity; twins; genetics; environment; attention*

INTRODUCTION

Mindfulness-based therapies have been found to be effective in treating internalizing disorders;[1–4] reducing both the symptoms of anxiety and depression, and

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the cognitive biases that play a central role in the etiology and maintenance of these problems.[5] Given the marked increase in depression prevalence during adolescence[6] and the plasticity during this period of brain maturation,[7,8] there is a growing interest in the application of mindfulness-based approaches in young people.[9]

Mindfulness refers to a wide range of constructs and can be studied as a psychological trait, with individuals differing in their dispositional level of mindfulness, and as a clinical intervention that aims to increase mindfulness for therapeutic purpose (e.g., mindfulness-based cognitive therapy). At its core trait mindfulness is characterized by nonjudgmental awareness of the present moment experience that is beneficial to psychological well-being.[10,11] It can therefore be defined both at an attentional level (awareness of the present moment) and the interpretation level (nonjudgmental and with acceptance).[12,13] Thus, mindfulness may influence cognitive processes at multiple stages, reducing attentional control deficits and negative cognitive styles that are central to mood disorders.[5,14–17] Measures of trait mindfulness tend to focus on the attentional processes, allowing investigations into whether improved attention control is one of the cognitive mechanisms that might explain this association.

Relatively little is known about the genetic and environmental influences on mindfulness. Individual differences in complex traits such as mindfulness are presumed to have arisen through an interaction of inherited predisposition and environmental circumstances, such as explicit training.[18] However, despite the clinical importance of trait mindfulness, the relative importance of genes, shared environment, and individual-specific experiences is unknown. It also remains to be investigated whether there are any differences in genetic or environmental influences on mindfulness between males and females.

Anxiety sensitivity is one cognitive bias that may play an important role in the association between mindfulness and depression. Anxiety sensitivity refers to an enhanced sensitivity (attentional bias) toward symptoms of anxiety, such as heart palpitations or worry, with a belief that these are harmful (interpretational bias).[19] Anxiety sensitivity is independently associated with both anxiety and depression across development.[20–22] Initial evidence suggests that one way trait mindfulness might benefit patients' well-being is by reducing the impact of anxiety sensitivity on their emotional distress.[23] Reduction of the cognitive biases such as anxiety sensitivity might be one of the cognitive mechanisms that explain the inverse association between mindfulness and depression. Individuals who score high on anxiety sensitivity have been found to exhibit less mindfulness, specifically showing difficulties with limiting attention to the current activity (attentional processing), and with experiencing the present state without evaluating or judging its content (interpretation).[23–25] This supports the view that mindfulness may be associated with reduction in cognitive biases such as anxiety sensitivity at both attentional and interpretational processing levels, which in turn might reduce internalizing symptoms.[26,27]

Examining genetic and environmental influences on the joint associations between trait mindfulness, depression, and anxiety sensitivity can help to clarify some of the mechanisms that underpin these relationships. One possibility may be that mindfulness, depression, and anxiety sensitivity share genetic influences. It is very common for traits that co-vary to have largely similar genetic factors that account for their co-occurrence, while nonshared environmental factors are generally smaller (the "generalist genes hypothesis").[28] We have previously shown that depressive symptoms and anxiety sensitivity share high and significant genetic correlations across development.[20,29] However, mindfulness is associated with a range of other traits, for example, self-esteem, physical well-being, and personality traits such as conscientiousness, agreeableness, and openness to experience.[10,30] Thus, genetic influences on mindfulness may be largely distinct from the ones influencing internalizing problems. Instead, environmental influences such as parenting or life events, may explain the relationship between mindfulness, depression, and anxiety sensitivity. Investigating the role of genes and environment in the relationship between mindfulness, depression, and anxiety sensitivity will help to understand the relative role of the biological and social mechanisms that link these traits.

The aim of the current study was to investigate the genetic and environmental influences on mindfulness, as well as on its associations with depressive symptoms and anxiety sensitivity. The current study focused specifically on the attentional control aspect of trait mindfulness.[31] Using a large epidemiological sample of 16-year-old twins, we first investigated the phenotypic correlations between trait mindfulness, depressive symptoms, and anxiety sensitivity. Second, we explored what proportion of variance in mindfulness was accounted for by genetic and environmental influences, and whether any sex differences in these influences were evident. Third, in order to understand the association of low mindfulness with depressive symptoms and anxiety sensitivity, we investigated genetic and environmental correlations shared between these traits. We hypothesized that our results would be in line with the "generalist genes hypothesis,"[28] resulting in high genetic and moderate environmental correlations. Finally, we were interested in the proportion of genetic and environmental influences on mindfulness not shared with depressive symptoms and anxiety sensitivity.

METHODS

PARTICIPANTS

The analyses use data from Twins Early Development Study (TEDS), a large epidemiological study of over 10,000 twin pairs born in England and Wales in 1994, 1995, and 1996. Full recruitment details are provided elsewhere.[32] The current analyses focus on the data

collected when twins were approximately 16 years old (mean age = 16.32, SD = .68 years). Informed consent was obtained from parents of all participating adolescents and the study was approved by the Institute of Psychiatry Ethics Committee. Zygosity was established using parent-report questionnaires of physical similarity, which is estimated to be 95% accurate when compared to DNA testing.[33] Where zygosity was ambiguous, DNA testing was conducted. The questionnaire booklets were returned by 10,320 individuals (55.51% female; 35.59% monozygotic (MZ), 32.51% same-sex dizygotic (DZ), 31.90% opposite-sex DZ twins). Participants were excluded if they did not provide consent, if they had severe medical disorders, experienced severe perinatal complications, or if their zygosity was unknown (N = 316 families). The sample size, internal consistencies, and descriptive statistics of all measures are presented in Table 1.

MEASURES

Mindfulness. Mindfulness was measured using a short version[31] of the Mindful Attention Awareness Scale (MAAS);[10] a 5-item self-report questionnaire focusing on statements relating attentional control (e.g., "I find myself doing things without paying attention"). Psychometric studies corroborate the utility of the shortened version of the MAAS scale.[31,34] Responses were summed to give total trait mindfulness scores; higher total scores reflect lower mindfulness.

Depression. Depressive symptoms were measured using the Short Mood and Feelings Questionnaire;[35] a 13-item self-report measure assessing how often depressive symptoms occurred in the past 2 weeks. Responses were summed to give total depressive symptoms scores. The measure demonstrates good reliability and validity.[35]

Anxiety sensitivity. Anxiety sensitivity was assessed using the Children's Anxiety Sensitivity Index;[36] an 18-item self-report questionnaire assessing fear of anxiety sensations (e.g., "It scares me when my heart beats fast"). The measure has sound psychometric properties.[36,37] Responses were summed to give total anxiety sensitivity scores.

ANALYSES

The twin design compares the degree of similarity between MZ (sharing 100% of their genes) and DZ (sharing on average 50% of their segregating genes) twin pairs. These relative differences in within-pair correlations allow estimations of the influences caused by additive genetics (A), shared environment (C), and nonshared environment (E). Where correlations are higher for MZ twins as compared to DZ pairs, genetic influence is assumed to be playing a role. Within-pair similarity that is not due to genetic factors is accounted for by shared environmental influences (C), which contribute to the resemblance between family members. C is evident when DZ correlations are more than half MZ correlations. Nonshared environment (E) accounts for individual-specific factors that create differences among siblings from the same family. These are estimated from within-pair differences between MZ twins. Any measurement error present is included in this term. Quantitative genetic designs and methods are described comprehensively elsewhere.[38]

All twin analyses were conducted using OpenMx[39] within R (www.R-project.org),[40] a structural equation modeling package for the analysis of genetically informative data that controls for nonindependence of family members. As is standard in model fitting analysis, the variables were regressed for age and sex,[41] and were mapped onto a standard normal distribution using the rank-based van der Waerden's transformation to correct for skew.

All models were fitted using raw data maximum likelihood. The core fit statistic was minus twice the log likelihood (−2LL) of the observations. This is not an overall measure of fit, but provides a relative measure of fit, since differences in −2LL between models are distributed as χ^2. Therefore, to examine the overall fit of the genetic model we compared the −2LL to that of a saturated model (one which fully describes data using the maximum number of free parameters, estimating variances, covariances, and means for the raw data to get a baseline index of fit). The fit of each submodel was assessed by χ^2 difference tests, Akaike's and Bayesian's information criterion (AIC = $\chi^2 - 2df$, BIC = $\chi^2 - k\ln(n)$) with lower χ^2 values, and more negative AIC and BIC values suggesting a better fit. If the difference between the AIC of two models was less than 10, the more parsimonious model was selected.[42] For all analyses, we also compared models with fewer parameters to the full A, C, and E correlated factors solution.

Univariate analyses assessing the influences of A, C, and E were conducted on all variables. Sex differences were examined to inform twin modeling. Qualitative sex differences were tested to see whether the same genetic and environmental sources contribute to individual differences in the phenotype for males and females. Second, quantitative sex differences were tested, where the same genetic and environmental sources operate, but they influence the phenotype in males and females to different degree. Third, we tested scalar sex differences, to investigate whether there is a scalar variance difference between males and females.

The Cholesky decomposition, represented as a multivariate correlated factors solution (Fig. 1a), was used to examine the genetic and environmental relationship between mindfulness, depressive symptoms, and anxiety sensitivity. The correlated factors solution assumes that each variable has unique A, C, and E influences, and that these trait-specific influences can be correlated with the A, C, and E influences

TABLE 1. Descriptive statistics, cross twin correlations, and univariate results

	Descriptive statistics				Cross twin correlations		Univariate influences		
	N (individuals)	Mean (SD), range	Skew	α	r_{MZ}	r_{DZ}	A	C	E
Mindfulness	2,118	8.96 (4.36), 0–23	−0.06	.76	.36 (.29–.42)	.14 (.10–.20)	.32 (.14–.41)	.02 (.00–.15)	.66 (.59–.74)
Depression	9,609	3.61 (4.41), 0–26	1.95	.88	.42 (.39–.45)	.21 (.20–.24)	.29 (.19–.38)	.12 (.05–.20)	.59 (.55–.63)
Anxiety sensitivity	9,608	7.95 (5.86), 0–36	1.14	.86	.46 (.43–.49)	.18 (.16–.20)	.36 (.27–.43)	.05 (.00–.12)	.59 (.56–.63)

Note: SD, standard deviation; α, internal consistency; MZ, monozygotic; DZ, dizygotic; A, additive genetic parameters; C, shared environmental parameters; E, nonshared environmental parameters.
Descriptive statistics and cross twin correlations are presented on untransformed and unregressed variables for comparison with other published samples. Univariate analyses are presented on transformed variables. 95% Confidence intervals (CIs) are presented in brackets. CIs not including 0 indicate significant estimates. Nonoverlapping CIs mean significant difference between the values. Some of the DZ correlations are less than half MZ correlations, suggesting that A should be interpreted as both additive and dominant genetic effects. Mindfulness was measured only in a subset of twins (a cohort born between January 1994 and August 1994), while depression and anxiety sensitivity was measured in the whole sample, resulting in larger sample sizes. All twins were approximately 16 years old at the time of data collection.

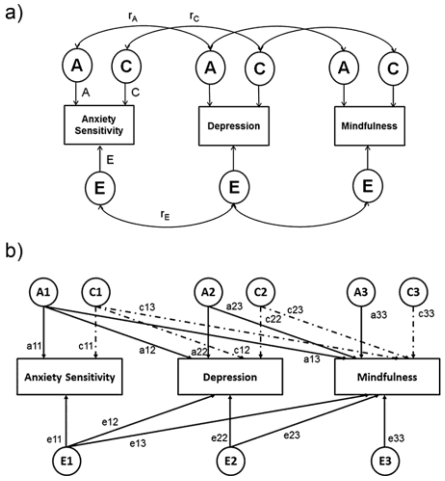

Figure 1. (a) Correlated factors solution; (b) Cholesky decomposition (attached separately).
***A*, additive genetic parameters; *C*, shared environmental parameters; *E*, non shared environmental parameters; r_A, genetic correlation; r_C, shared environmental correlation; r_E, nonshared environmental correlation; a11–a33, genetic influences; c11–c33, shared environmental influences; e11–e33, nonshared environmental influences.**

on other traits (r_A = genetic correlation, r_C = shared environmental correlation, and r_E = nonshared environmental correlation). The proportions of the phenotypic correlations accounted for by *A*, *C*, and *E* influences were also calculated. The data were additionally interpreted as the Cholesky decomposition (Fig. 1b), which assumes three distinct sets of genetic and environmental influences on each variable. A1, C1, and E1 are common factors influences on the first variable via paths a11, c11, and e11 that can also influence the remaining two variables via paths a12, a13, c12, c13, e12, and e13. A2, C2, and E2 influence the second variable via paths a22, c22, and e22 and can also influence the third variable via paths a23, c23, and e23, over and above the influences accounted for by A1, C1, and E1. A3, C3, and E3 are specific influences unique to the third variable only (via paths a33, c33, and e33). Total *A*, *C*, and *E* effects on each individual measure can be obtained by summing all paths to that measure (e.g., total genetic influences on the third variable can be obtained by adding influences from paths a13, a23, and a33). Although any ordering of the variables explains the variance–covariance matrix between variables equally well, mindfulness was placed as the last variable as the aim was to investigate whether there are any specific genetic or environmental influences on mindfulness, over and above those shared with depressive symptoms and anxiety sensitivity. Due to interpretational constraints,[43] only the specific influences on mindfulness are presented and interpreted (paths a33, c33, and e33).

RESULTS

The descriptive statistics for all measures, such as means, standard deviations, and skew, are presented in Table 1. Females scored significantly higher on all scales than males (mindfulness: $t(2116) = 3.22$, $P < .05$, $d = .14$; depression: $t(9607) = 19.96$, $P < .05$, $d = .41$; anxiety sensitivity: $t(9606) = 29.06$, $P < .05$, $d = .59$), suggesting that on average females had lower mindfulness and higher depressive symptoms and anxiety sensitivity than males (Supporting Information Table A1). Low mindfulness was moderately correlated with depressive symptoms and anxiety sensitivity (r_{pb} = .34 with both, Table 2). Depressive symptoms and anxiety sensitivity were also correlated (r_{pb} = .48, Table 2). Of note, some of the DZ correlations were less than half MZ correlations (Tables 1 and 2), suggesting that *A* should be interpreted as both additive and dominant genetic effects.

Univariate twin modeling results (Table 1) revealed that mindfulness was moderately influenced by genetic ($A = .32$) and nonshared environmental influences ($E = .66$), with no significant influence of shared environment. *A* similar pattern was found for genetic and environmental influences on depressive symptoms and anxiety sensitivity ($A = .29$ and .36, respectively, $E = .59$ for both). At the univariate level, scalar (variance) sex differences were found for both depressive symptoms and anxiety sensitivity. In addition, quantitative sex differences were evident for depression. There were no qualitative sex differences in our sample and these sex differences were not modeled further. At the multivariate level, first a model allowing for quantitative sex differences was fitted, followed by a scalar multivariate model where estimates were equated across sex, with a scalar variable modeled to account for the variance difference in depression and anxiety sensitivity. As estimates were similar for males and females (see Supporting Information Table A2), the scalar model that estimates one set of values for the whole sample is presented here. Model fit comparisons revealed that *C* could be dropped from the multivariate model without significant deterioration of the fit (Table 3).

Low mindfulness had significant moderate genetic correlations and small nonshared environmental correlations with depressive symptoms and anxiety sensitivity ($r_A = .52$ and .53, respectively, $r_E = .22$ for both, Table 2). Depressive symptoms and anxiety sensitivity showed moderate genetic and nonshared environmental correlations ($r_A = .67$ and $r_E = .34$). Genetic influences accounted for over half of the phenotypic correlations between the variables (Table 2).

The Cholesky decomposition revealed that about two-thirds of genetic influences and almost all nonshared environmental influences on mindfulness are independent of the influences on depressive symptoms and anxiety sensitivity (specific influences on mindfulness: $a33 = \sqrt{.23}$, CI: .16–.30; and $e33 = \sqrt{.61}$, CI: .54–.68).

DISCUSSION

This is the first study to investigate the genetic and environmental underpinnings of trait mindfulness and

TABLE 2. Multivariate results—phenotypic, genetic, and nonshared environmental correlations, and proportion of phenotypic correlation explained by *A* and *E*

	Cross twin cross trait correlations		Phenotypic, genetic and environmental correlations			Proportion of the phenotypic correlation explained by *A* and *E*	
	r_{MZ}	r_{DZ}	r_{pb}	r_A	r_E	*A*	*E*
Mindfulness–depression	.20 (.15–.28)	.06 (.01–.11)	.34 (.30–.37)	.52 (.40–.64)	.22 (.15–.29)	.60 (.47–.72)	.40 (.28–.53)
Mindfulness–anxiety sensitivity	.19 (.12–.26)	.10 (.05–.15)	.34 (.30–.38)	.53 (.39–.66)	.22 (.15–.30)	.59 (.44–.73)	.41 (.27–.56)
Depression–anxiety sensitivity	.31 (.28–.34)	.15 (.13–.17)	.48 (.47–.50)	.67 (.63–.72)	.34 (.31–.37)	.60 (.55–.64)	.40 (.36–.45)

Note: MZ, monozygotic, DZ, dizygotic, r_{pb}, phenotypic correlation; r_A, genetic correlation; r_E, nonshared environmental correlation; *A*, additive genetic parameters; *E*, nonshared environmental parameters.
95% Confidence intervals (CIs) are presented in brackets. CIs not including 0 indicate significant estimates. Nonoverlapping CIs mean significant difference between the values. Some of the DZ correlations are less than half MZ correlations, suggesting that *A* should be interpreted as both additive and dominant genetic effects. Partial correlations revealed that mindfulness was independently associated with depression ($r = .22$ (95% CIs: .18–.26)) and anxiety sensitivity ($r = .17$ (95% CIs: .13–.21)). Furthermore, controlling for mindfulness significantly reduced the correlation between depression and anxiety sensitivity ($r = .43$ (95% CIs: .41–.45)), suggesting that mindfulness might play a role in the relationship between the anxiety sensitivity and depression. AE models are presented, as *C* influences were small and not significant (except depression), and were dropped from the model without a significant deterioration of the fit (Table 3). The results of the full ACE model are presented in the appendix (Supporting Information Table A3).

its relationship with depression and anxiety sensitivity. Quantitative genetic analysis revealed that mindfulness is influenced by both genetic and nonshared environmental factors, with no influence of shared environmental factors. Common genetic influences were found to explain most of the moderate association between low mindfulness, depressive symptoms, and anxiety sensitivity. Despite the significant genetic and environmental associations with depressive symptoms and anxiety sensitivity, mindfulness was also characterized by unique genetic and environmental influences.

Phenotypic analyses confirmed previous findings that low mindfulness is associated with both depressive symptoms[44] and anxiety sensitivity.[23–25] The mindfulness measure used in the current study focuses specifically on the attentional aspect of this trait. The shared genetic and environmental risk for depression, anxiety sensitivity, and our attentional measure of low mindfulness is in line with the evidence that cognitive impairment, including attentional control deficits, is an important aspect of depression[16,17] and of anxiety sensitivity. The mental concerns dimension of anxiety sensitivity that measures worry regarding cognitive control was found to be particularly strongly associated with depression,[20] suggesting that concerns about own attentional performance may be an important content of the cognitive biases in depressed individuals. Furthermore, a recent study showed that improvements in attentional control following mindfulness training were associated with reductions in depressive symptoms.[26]

TABLE 3. Multivariate model fit statistics

	−2LL	*df*	χ^2	Δ*df*	*P*	AIC	Size-adjusted BIC
(a) Comparison to saturated model							
Saturated model	54727.96	21200				12327.96	55451.66
Correlated factors solution (ACE)	55298.39	21312	570.43	112	<.05	12674.39	55421.69
(b) Comparison to correlated factors solution (ACE)							
Correlated factors solution (AE)	55309.93	21318	11.54	6	0.07	12673.93	55401.06
Correlated factors solution (CE)	55386.44	21318	88.05	6	<.05	12750.44	55477.57
Correlated factors solution (*E*)	56213.32	21324	914.93	12	<.05	13565.32	56272.29

Note: −2LL, minus twice the log likelihood; *df*, degrees of freedom; *P*, probability; AIC, Akaike's information criterion; BIC, Bayesian's information criterion.
The correlated factors solution did not fit as well as the saturated model. This occurs frequently in studies with very large sample sizes because minimal variance differences between groups can be highly statistically significant. The best fitting model (correlated factors solution, AE) was selected based on the principle of parsimony and lowest AIC and BIC value. A difference in AIC between two models of 2 or less, provides equivalent support for both models (in which case the most parsimonious model should be chosen), a difference of 3 indicates that the lower AIC model has considerably more support, and a difference of more than 10, indicates that the lower AIC model is a substantially better fit compared to the higher AIC model.[42] For completeness, the results of the full ACE model are presented in the appendix (Supporting Information Table A3).

Given that adolescence is a period of heightened brain plasticity,[7] mindfulness might be especially useful in depression prevention and treatment in young people by means of improving attentional control.[9] However, due to the cross-sectional nature of the data, the direction of the associations and the possible causal links between mindfulness, depression, and anxiety sensitivity need to be explored in future longitudinal studies. Furthermore, genetically sensitive interventions are needed to investigate how the role of genes and environment in mindfulness and its etiological relationship with anxiety sensitivity and depression might change due to an intervention.[45]

The univariate twin modeling results highlight the role of both genetic and individual-specific environmental influences in adolescent mindfulness. Environmental factors might include parenting, life events, cultural exposure, and meditation-related training. Future research focused on identifying these environmental factors may inform targeted clinical and resilience interventions in adolescence. We did not find evidence for a role of shared environmental influences on trait mindfulness, suggesting that environmental factors are individual specific. This might be because shared environmental influences are thought to play a diminishing role in adolescence and adulthood.[38] It would be interesting to investigate the genetic and environmental influences on mindfulness in younger age groups, when trait mindfulness emerges and when the earliest mindfulness-based interventions may be implemented.[9,46,47] We found that on average females were less mindful than males; however, we did not find evidence for sex differences in the etiology of mindfulness. Sex differences are rarely examined in mindfulness, so these results warrant further investigation.

Multivariate twin modeling analyses revealed that mindfulness, depressive symptoms, and anxiety sensitivity share moderate genetic and small nonshared environmental correlations. Furthermore, we found that genetic influences account for over half of the moderate phenotypic association between mindfulness, depressive symptoms, and anxiety sensitivity. Thus, as expected, the association between mindfulness and these internalizing problems is explained largely by underlying genetic liability, in line with the "generalist genes hypothesis."[28] The results are suggestive of a biological pathway linking mindfulness, depression, and anxiety sensitivity. Recent studies point to epigenetic regulation of inflammatory pathways as one of the biological mechanisms underpinning the mindfulness-based interventions.[48] The biological pathways associated with mindfulness that may benefit mental health could include positive regulation of brain, endocrine, and immune function.[49]

Despite its etiological links with depressive symptoms and anxiety sensitivity, mindfulness is characterized by significant unique influences, with about two-thirds of genetic factors and almost all nonshared environmental factors being independent of depressive symptoms and anxiety sensitivity. It is in line with a growing body of research suggesting that mindfulness is associated with a range of other constructs over and above its link with depressive symptoms and anxiety sensitivity.[10,30] Overall, the current study adds to the evidence that above its role in mood problems, mindfulness might also be characterized by unique developmental patterns and protective factors worth investigating.

LIMITATIONS

The large, genetically-informative sample is the strength of the study. However, a number of limitations are worth noting. First, it remains debated whether mindfulness can be accurately assessed using self-report questionnaires, and it is suggested that it may be better captured by measures such as interviews.[50] Although there are no objective markers of mindfulness that the questionnaires could be validated against, self-report mindfulness is negatively associated with behavioral measures of related constructs, such as mind wandering[51] and attention lapses.[52] An additional limitation of self-report data is that it could have inflated nonshared environmental correlations due to shared measurement error. Second, the current study used a relatively narrow definition of mindfulness in terms of attentional processing, but it did not measure other facets of the trait, such as the nonjudgmental and accepting attitude.[50] This somewhat limits the interpretability of the currents results and mindfulness as a broader and multifactorial concept remains to be investigated in future twin studies. However, the focus on attentional control allowed more precise investigations of one specific cognitive mechanism central to mindfulness and its association with depression and anxiety sensitivity. Similarly, the relatively narrow age-range of the current sample limits the generalizability of the results to other ages, although the etiology of depression and anxiety sensitivity is not expected to change markedly across adolescence.[53,54] Furthermore, the precise age-range allows closer understanding of a specific developmental stage. Future research should elucidate etiology of mindfulness across development to further inform this debate. Finally, there are a number of limitations inherent to the twin design, comprehensively discussed elsewhere.[38] These limitations have minimal and contrasting effects but suggest that parameter estimates should be taken as indicative rather than absolute values.

CONCLUSIONS

The present study is the first to show that both nature and nurture play an important role in adolescent mindfulness. Future research should focus on elucidating the specific environmental factors that promote trait mindfulness across development. Furthermore, the current study revealed shared genetic influences underpinning the associations between mindfulness, depressive symptoms, and anxiety sensitivity, and suggests that attention control may be a key cognitive mechanism that explains this association. Future research should focus on examining the specific biological pathways underlying this

association. Finally, the evidence of a significant proportion of unique genetic and environmental influences on mindfulness suggests largely independent influences on this trait.

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REFERENCES

1. Chiesa A, Serretti A. A systematic review of neurobiological and clinical features of mindfulness meditations. Psychol Med 2010;40(08):1239–1252.
2. Keng S-L, Smoski MJ, Robins CJ. Effects of mindfulness on psychological health: A review of empirical studies. Clin Psychol Rev 2011;31(6):1041–1056.
3. Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and depression: a meta-analytic review. J Consult Clin Psychol 2010;78(2):169–183.
4. Chen KW, Berger CC, Manheimer E, et al. Meditative therapies for reducing anxiety: a systematic review and meta-analysis of randomized controlled trials. Depress Anxiety 2012;29(7):545–562.
5. Mathews A, MacLeod C. Cognitive vulnerability to emotional disorders. Annu Rev Clin Psychol 2005;1:167–195.
6. Hankin BL, Abramson LY, Moffitt TE, Silva A, McGee R, Angell KE. Development of depression from preadolescence to young adulthood: emerging gender differences in a 10-year longitudinal study. J Abnorm Psychol 1998;107:128–140.
7. Blakemore S-J. The social brain in adolescence. Nat Rev Neurosci 2008;9(4):267–277.
8. Kadosh KC, Linden DE, Lau JY. Plasticity during childhood and adolescence: innovative approaches to investigating neurocognitive development. Dev Sci 2013;16(4):574–583.
9. Burke CA. Mindfulness-based approaches with children and adolescents: a preliminary review of current research in an emergent field. J Child Fam Stud 2010;19(2):133–144.
10. Brown KW, Ryan RM. The benefits of being present: mindfulness and its role in psychological well-being. J Pers Soc Psychol 2003;84(4):822–848.
11. Bishop SR, Lau M, Shapiro S, et al. Mindfulness: a proposed operational definition. Clin Psychol Sci Prac 2004;11(3):230–241.
12. Shapiro SL, Oman D, Thoresen CE, Plante TG, Flinders T. Cultivating mindfulness: effects on well-being. J Clin Psychol 2008;64(7):840–862.
13. Lang AJ. What mindfulness brings to psychotherapy for anxiety and depression. Depress Anxiety 2013;30(5):409–412.
14. Jacobs RH, Reinecke MA, Gollan JK, Kane P. Empirical evidence of cognitive vulnerability for depression among children and adolescents: a cognitive science and developmental perspective. Clin Psychol Rev 2008;28(5):759–782.
15. Mor N, Winquist J. Self-focused attention and negative affect: a meta-analysis. Psychol Bull 2002;128(4):638–662.
16. Snyder HR. Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. Psychol Bull 2013;139(1):81–132.
17. Teachman BA, Joormann J, Steinman SA, Gotlib IH. Automaticity in anxiety disorders and major depressive disorder. Clin Psychol Rev 2012;32(6):575–603.
18. Davidson RJ. Empirical explorations of mindfulness: conceptual and methodological conundrums. Emotion 2010;10(1):8–11.
19. Taylor S. Anxiety Sensitivity: Theory, Research and Treatment of the Fear of Anxiety. Mahwah, NJ: Lawrence Erlbaum Associates; 1999.
20. Brown HM, Waszczuk MA, Zavos HMS, Trzaskowski M, Gregory AM, Eley TC. Cognitive content-specificity in anxiety and depressive disorder symptoms: a twin study of cross-sectional associations with anxiety sensitivity dimensions across development. Psychol Med.
21. Naragon-Gainey K. Meta-analysis of the relations of anxiety sensitivity to the depressive and anxiety disorders. Psychol Bull 2010;136(1):128–150.
22. Noël VA, Francis SE. A meta-analytic review of the role of child anxiety sensitivity in child anxiety. J Abnorm Child Psychol 2011;39(5):721–733.
23. McCracken LM, Keogh E. Acceptance, mindfulness, and values-based action may counteract fear and avoidance of emotions in chronic pain: an analysis of anxiety sensitivity. J Pain 2009;10(4):408–415.
24. Vujanovic AA, Zvolensky MJ, Bernstein A, Feldner MT, McLeish AC. A test of the interactive effects of anxiety sensitivity and mindfulness in the prediction of anxious arousal, agoraphobic cognitions, and body vigilance. Behav Res Ther 2007;45(6):1393–1400.
25. McKee L, Zvolensky MJ, Solomon SE, Bernstein A, Leen-Feldner E. Emotional-vulnerability and mindfulness: a preliminary test of associations among negative affectivity, anxiety sensitivity, and mindfulness skills. Cogn Behav Ther 2007;36(2):91–101.
26. Chambers R, Gullone E, Allen NB. Mindful emotion regulation: an integrative review. Clin Psychol Rev 2009;29(6):560–572.
27. Joormann J, Quinn ME. Cognitive processes and emotion regulation in depression. Depress Anxiety 2014;31(4):308–315.
28. Eley TC. General genes: a new theme in developmental psychopathology. Curr Dir Psychol Sci 1997;6:90–95.
29. Zavos H, Rijsdijk FV, Gregory AM, Eley TC. Genetic influences on the cognitive biases associated with anxiety and depression symptoms in adolescents. J Affect Disord 2010;124(1):45–53.
30. Giluk TL. Mindfulness, big five personality, and affect: a meta-analysis. Pers Individ Dif 2009;47(8):805–811.
31. Van Dam NT, Earleywine M, Borders A. Measuring mindfulness? An item response theory analysis of the mindful attention awareness scale. Pers Individ Dif 2010;49(7):805–810.

32. Haworth CMA, Davis OSP, Plomin R. Twins Early Development Study (TEDS): a genetically sensitive investigation of cognitive and behavioral development from childhood to young adulthood. Twin Res Hum Genet 2013;16(1):117–125.
33. Price TS, Freeman B, Craig IW, Petrill SA, Ebersole L, Plomin R. Infant zygosity can be assigned by parental report questionnaire data. Twin Res 2000;3:129–133.
34. Black DS, Sussman S, Johnson CA, Milam J. Psychometric assessment of the mindful attention awareness scale (MAAS) among Chinese adolescents. Assessment 2012;19(1):42–52.
35. Angold A, Costello EJ, Messer SC, Pickles A, Winder F, Silver D. The development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. Int J Methods Psychiatr Res 1995;5:1–12.
36. Silverman W, Fleisig W, Rabian B, Peterson R. Childhood anxiety sensitivity index. J Clin Child Adolesc Psychol 1991;20(2):162–168.
37. Reiss S, Peterson R, Gursky D, McNally R. Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. Behav Res Ther 1986;24(1):1–8.
38. Plomin R, DeFries JC, Knopik VS, Neiderhiser JM. Behavioral Genetics. 6th ed. New York: Worth Publishers; 2013.
39. Boker S, Neale M, Maes H, et al. OpenMx: an open source extended structural equation modeling framework. Psychometrika 2011;76(2):306–317.
40. TeamRDC. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2010.
41. McGue M, Bouchard TJ, Jr. Adjustment of twin data for the effects of age and sex. Behav Genet 1984;14(4):325–343.
42. Wagenmakers E-J, Farrell S. AIC model selection using Akaike weights. Psychon Bull Rev 2004;11(1):192–196.
43. Loehlin JC. The Cholesky approach: a cautionary note. Behav Genet 1996;26(1):65–69.
44. Cash M, Whittingham K. What facets of mindfulness contribute to psychological well-being and depressive, anxious, and stress-related symptomatology? Mindfulness 2010;1(3):177–182.
45. Haworth CM, Davis OS. From observational to dynamic genetics. Front. Genet. 2014;5(6):1–7.
46. Napoli M, Krech PR, Holley LC. Mindfulness training for elementary school students: the attention academy. J Appl School Psychol 2005;21(1):99–125.
47. Lee J, Semple RJ, Rosa D, Miller L. Mindfulness-based cognitive therapy for children: results of a pilot study. J Cogn Psychother 2008;22(1):15–28.
48. Kaliman P, Álvarez-López MJ, Cosín-Tomás M, Rosenkranz MA, Lutz A, Davidson RJ. Rapid changes in histone deacetylases and inflammatory gene expression in expert meditators. Psychoneuroendocrinology 2014;40:96–107.
49. Ludwig DS, Kabat-Zinn J. Mindfulness in medicine. JAMA 2008;300(11):1350–1352.
50. Grossman P. Defining mindfulness by how poorly I think I pay attention during everyday awareness and other intractable problems for psychology's (re) invention of mindfulness: comment on Brown et al. (2011). Psychol Assess 2011;23(4):1034–1040.
51. Mrazek MD, Smallwood J, Schooler JW. Mindfulness and mind-wandering: finding convergence through opposing constructs. Emotion 2012;12(3):442–448.
52. Cheyne JA, Carriere JS, Smilek D. Absent-mindedness: lapses of conscious awareness and everyday cognitive failures. Conscious Cogn 2006;15(3):578–592.
53. Zavos HMS, Gregory AM, Eley TC. Longitudinal genetic analysis of anxiety sensitivity. Dev Psychol 2012;48(1):204–212.
54. Bergen SE, Gardner CO, Kendler KS. Age-related changes in heritability of behavioral phenotypes over adolescence and young adulthood: a meta-analysis. Twin Res Hum Genet 2007;10(03):423–433.

7. CHAPTER 7 - ATTENTIONAL CONTROL THEORY IN MIDDLE CHILDHOOD: ENHANCED ATTENTIONAL CAPTURE BY NON-EMOTIONAL AND EMOTIONAL DISTRACTORS IN ANXIETY AND DEPRESSION

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Supplementary materials for this chapter are presented in **Appendix E**

7.1. ABSTRACT

Attentional control theory (ACT) proposes that anxiety is associated with executive functioning deficits. The theory has been widely investigated in adults. The current study tested whether symptoms of childhood anxiety and depression were associated with experimentally measured attentional control in the context of non-emotional and emotional stimuli. Sixty-one children (mean age = 9.23 years, range = 8.39 - 10.41) reported their trait anxiety and depression symptoms and completed three visual search tasks. The tasks used a variant of an irrelevant singleton paradigm and measured attentional capture by task-irrelevant non-emotional (color) and emotional (facial expressions) distractors. Significant attentional capture by both non-emotional and emotional distractors was observed, and was significantly correlated with trait anxiety and symptoms of depression. The strength of relationship between attentional capture and the symptoms did not differ significantly for non-emotional and emotional distractors. The results suggest that symptoms of childhood anxiety and depression are associated with poorer attentional control both in the presence of emotional and non-emotional stimuli, supporting ACT in younger populations. This attentional deficit in the context of non-emotional information might be as central to childhood internalizing symptoms as attentional biases often observed on tasks investigating processing of emotional stimuli.

7.2. INTRODUCTION

Anxiety and depression are highly prevalent and frequently co-occur across the lifespan (Angold, Costello, & Erkanli, 1999; Kessler, Chiu, Demler, Merikangas, & Walters, 2005). Both disorders have an early age of onset, are very common in young people (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Kessler, Berglund, et al., 2005; Kessler, Chiu, et al., 2005) and reliably predict long-term mental health difficulties (Gregory et al., 2007; Rutter, Kim-Cohen, & Maughan, 2006). Biases in how individuals attend to, interpret and remember emotional information (particularly negative information) have been implicated in the development and maintenance of internalizing symptoms and disorders (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van Ijzendoorn, 2007; Jacobs, Reinecke, Gollan, & Kane, 2008; Mathews & MacLeod, 2005; Muris & Field, 2008). These cognitive biases are also targeted by interventions such as cognitive-behavioral therapy (CBT), a recommended first-line treatment for both anxiety and depression (AACAP, 2007a, 2007b).

Recent research has begun to investigate attentional processing of non-emotional information in anxious and depressed individuals. Dual-processing theories posit that attentional selection is determined by the competition of two attentional systems: a stimulus-driven, bottom-up system, and a volitional, top-down system (Corbetta & Shulman, 2002; Posner & Petersen, 1990). Attentional dysregulation may underlie internalizing disorders (Cisler & Koster, 2010). Attentional control theory (ACT) proposes that trait anxiety impairs the efficiency of the volitional system, with bottom-up attentional selection mechanisms overpowering the top-down control system (Derakshan & Eysenck, 2009; Eysenck, Derakshan, Santos, & Calvo, 2007). As a result, anxious individuals are thought to have poorer inhibitory abilities and show more distractibility than non-anxious individuals. ACT is widely supported using non-emotional experimental tasks in adults with anxiety (Derakshan & Eysenck, 2009; Eysenck & Derakshan, 2011), and is also implicated in adults with depression symptoms (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008; Joormann & Gotlib, 2010; Snyder, 2013).

Furthermore, attentional control serves as a regulatory top-down mechanism moderating emotional attentional biases, with some evidence that biases are only observed in adults with anxiety who show poor attentional control (Derryberry & Reed, 2002; Reinholdt-Dunne, Mogg, & Bradley, 2009). Thus, general attentional control deficits might in part explain some of the cognitive biases commonly observed on emotional tasks with adults.

There is a growing interest in investigating the relationship between attentional control, internalizing symptoms and cognitive biases in younger populations. Limited empirical evidence indicates an association between poor attentional control and internalizing symptoms in children (Eisenberg et al., 2001; Hughes & Ensor, 2011; Muris, Meesters, & Rompelberg, 2007). These results are in line with ACT, suggesting that bottom-up attentional capture overpowers top-down control in children with symptoms of anxiety and depression. Furthermore, high negative emotionality combined with low attentional control was associated with the highest levels of internalizing problems, indicating a moderating effect of attentional control (Lonigan & Vasey, 2009; Salemink & Wiers, 2012; Susa, Pitică, Benga, & Miclea, 2012). However, many studies used self-reported attentional control, which may be considered a limitation given that questionnaire measures of attentional control generally do not reflect observed behavioral measures of attentional control (Muris, van der Pennen, Sigmond, & Mayer, 2008; Reinholdt-Dunne et al., 2009). Previous research using experimental methods (Hughes & Ensor, 2011; Muris et al., 2008; Salemink & Wiers, 2012) have tended to use relatively complex measures of attentional processes, such as the Stroop task, which are thought to involve various constituents of information-processing, making it difficult to determine which one is associated with internalizing symptoms. Thus, there is a need for a simple experimental attentional control task to study ACT in childhood.

The irrelevant singleton method (Theeuwes, 1991, 1992), a relatively pure measure of attentional control, attempts to measure whether the bottom-up system is more dominant than the top-down system during initial attention competition. Participants perform a visual

search for a target odd shape in an array of shapes, but on 50% of trials a salient, task-irrelevant color distractor is present. Identification of the unique shape that is unaffected by whether the task-irrelevant distractor is present or not indexes a dominant top-down system. Conversely, the slowing caused by the presence of a distractor indexes the amount of attentional capture via the bottom-up system, providing a direct measure of inhibitory attentional control (Theeuwes, 2010). Recent electrophysiological studies with adults indicate that reaction times are not confounded by other processes such as decision making or response generation, confirming this task is a specific measure of top-down filtering mechanisms (Hickey, McDonald, & Theeuwes, 2006; Moran & Moser, 2014). This measure was significantly correlated with trait anxiety (Moran & Moser, 2014; Moser, Becker, & Moran, 2012) and symptoms of depression and PTSD (Esterman et al., 2013) in adults, supporting ACT.

The current study investigated the relationship between attentional control and symptoms of anxiety and depression in school-aged children. First, attentional control was examined using a standard shape version of the irrelevant singleton task to establish whether experimentally measured attentional control was associated with internalizing symptoms in childhood as indicated in limited studies with largely self-reported attentional control in children. Second, the irrelevant singleton task was adapted to include face stimuli instead of shapes, and participants were asked to search for an odd gender face (rather than an odd shape) in the array. This task (hereafter referred to as the faces-color task) examined whether a task-irrelevant color distractor (an odd colored face) produces attentional capture when performing a visual search amongst face stimuli, and whether this attentional capture is also associated with internalizing symptoms. The third task (referred to as the faces-valence task) also required participants to search for an odd gender face and investigated whether task-irrelevant *emotional* distractors (an odd valenced facial expression; e.g. an angry face amongst an array of neutral faces) elicit attentional capture that is associated with internalizing symptoms. We hypothesized that there would be attentional capture by non-emotional and

emotional distractors for visual search among faces, and that greater attentional capture on both face tasks would be associated with symptoms of anxiety and depression. Finally, we compared the magnitude of attentional capture by non-emotional (color) and emotional (face expression) distractors, and their associations with internalizing symptoms. If poor attentional control is as central to childhood anxiety and depression as the attentional biases typically observed on emotional tasks, we expected that attentional capture due to non-emotional and emotional distractors would be similarly associated with internalizing symptoms.

7.3. METHODS

7.3.1. PARTICIPANTS

Ethical approval was granted by the Psychiatry, Nursing and Midwifery Research Ethics Subcommittee of King's College London (ref no: PNM/12/13-54). Participants were recruited from a primary school in London, UK. Written consent was obtained from parents and verbal assent from children. Sixty-one children (mean age=9.23 years, SD=.57, range: 8.39-10.41) participated (34% response rate) of which 52.46% were male, 95.08% right-handed and 90.20% classified as Caucasian; which is comparable to the UK general population (Scott, Pearce, & Goldblatt, 2001).

7.3.2. STIMULI AND MATERIALS

Questionnaires

Trait anxiety was assessed using the Trait Anxiety Inventory for Children (STAIC-T) (Spielberger, 1973). Children indicated using keyboard buttons how often (hardly ever, sometimes, often) the 20 questionnaire items were true for them. Depression symptoms were assessed using the Short Mood and Feelings Questionnaire (SMFQ) (Angold et al., 1995), a 13-item self-report

measure assessing whether (not true, sometimes, true) symptoms of depression occurred in the previous two weeks. Higher scores indicate higher trait anxiety and depression symptoms, respectively. The psychometric properties of both measures are very good (Angold et al., 1995; Finch Jr, Montgomery, & Deardorff, 1974; Papay & Hedl Jr, 1978) and the internal consistencies in the current study were high (α=.85 and .81 for STAIC-T and SMFQ respectively). Anxiety and depression were highly correlated (*r*=.70, *p*<.001**).** Additionally, in order to capture overall emotional problems, a composite internalizing score was formed with unit-weighted z-scores of anxiety and depression measures.

Attentional Tasks

Shapes task

The shapes task was adapted from a study in adults (Moser et al., 2012). Ten shape outline stimuli (diamonds and circles) were presented in random order spaced in an imaginary circle around a fixation point on a black background (Figure 7.1a). The shapes always contained a grey line segment presented centrally. The line segments were oriented vertically, horizontally, or tilted 22.5° to the right or left of the horizontal or vertical plane. The search array comprised 9 identical shapes and 1 odd target shape (e.g. a diamond amongst circles for 50% of trials and a circle amongst diamonds on the other 50%). The odd target shape contained vertical lines on 50% of the trials, and horizontal lines on the remaining trials (randomly assigned), while the rest of the array shapes contained the randomly assigned tilted line segments. Half of all trials contained no distractor; all 10 shapes were the same color (either green or red). The distractor trials were identical, but one of the nine non-target shapes was selected at random to appear in the opposite color to the other shapes. Participants were required to find the odd shape in the array and identify whether the line inside was horizontal or vertical.

Faces-color task

The aim of the faces-color task was to establish whether there is attentional capture by an irrelevant color singleton amongst an array of face stimuli. The shape stimuli were substituted with two faces selected from the NimStim face set (Tottenham et al., 2009). The faces-color task is a novel adaptation of the shapes task with two modifications. Participants were required to find the odd gender face in the array, and identify whether the line next to the odd gender face was horizontal or vertical. On 50% of trials a single male face target appeared amongst 9 identical female faces and vice versa for the remaining 50% of trials. The faces were shaded green or red, and on distractor trials (50% of all trials) one face appeared in the opposite color. The line segments were presented next to the face in an outer circle in order to not interfere with the face image (Figure 7.1b).

Trials were randomly presented in two blocks, one with all emotionally neutral faces and one where all faces had an angry facial expression. Both blocks were used so that faces-color and faces-valence task (see below) contained identical no-distractor trials and were counterbalanced on facial expressions used, allowing for direct comparison between the two tasks. The identity of the male and female face remained constant across blocks.

Faces-valence task

The aim of the faces-valence task was to establish whether there is attentional capture by an irrelevant emotional singleton amongst an array of face stimuli, and whether the magnitude of this 'emotional' capture differs from the extent of attentional capture by a color distractor amongst an array of face stimuli on the faces-color task. In this task, participants were again required to identify whether the line next to the odd gender face was horizontal or vertical. However, instead of the presence of a color-face distractor, there was a facial expression distractor. On the no-distractor trials (50% of all the trials), all 10 faces shared the same facial expression (either neutral or angry). The distractor trials were identical, but one of the nine

non-target faces was randomly selected to appear in the opposite facial expression to the other faces. For example, if nine faces had a neutral expression (eight identical female faces and one target male face, all the same color), the distractor face had an angry expression (an angry female face of the same identity and color as the remaining female faces). Thus, half the trials consisted of an angry distractor amongst neutral faces, and half consisted of a neutral distractor amongst angry faces (Figure 7.1c).

Trials were presented in two blocks in randomized order; one with all green faces and one with all red faces. Both blocks were used so that faces-color and faces-valence tasks contained identical no-distractor trials and were counterbalanced on colors used, allowing for direct comparison between the two tasks. As with the faces-color task, the identity of the male and female face remained constant across blocks.

7.3.3. PROCEDURE

All tasks were programmed in E-Prime 2.0 (Psychology Software Tools, Pittsburgh, PA). Children were supervised by a researcher during a 1 hour session undertaken individually in a quiet classroom. Instructions and questionnaire items were read aloud to ensure comprehension. The children and the school each received a voucher for participating.

The questionnaires were completed first in a randomized order, followed by the three experimental tasks. For comparison with other published studies, the shapes task was always completed first, to prevent introducing potential carry over effects of the face task. The four blocks of face tasks (two for the faces-color task and two for the faces-valence task) were presented next, in a randomized order.

The images were displayed on a laptop (13.3'' display with 1366 x 768 screen resolution) and each image was size 130×178 pixels. Children were instructed to press a button on a keyboard (L for 'horizontal', A for 'vertical', both labelled clearly) to indicate whether the line segment

belonging to the target shape or face was horizontally or vertically oriented. In accordance with previous research using the irrelevant singleton task (Moser et al., 2012), they were instructed to ignore any color/facial expression information and focus solely on finding the odd shape/gender face. Reaction time (RT) was recorded. Each task consisted of 160 trials, with complete counterbalancing of the 10 target locations × 2 target line orientations × 2 target shape colors/face colors/face expressions × 2 target shape/gender face × 2 distractor conditions. On distractor trials, the distractor location was random. Across the three tasks participants completed 480 trials in total, with breaks in-between blocks and tasks.

Each trial began with a fixation point presented for a randomly selected time ranging from 600-1200ms in 100ms increments, followed by a search array displayed until the participant responded. Auditory feedback (a short beep sound) was given for incorrect responses. The next trial began after a 1 second black frame.

7.3.4. DATA PREPARATION AND ANALYSIS STRATEGY

For comparison with published studies, where possible the analyses followed a previously used approach (Moser et al., 2012). Task accuracy on all tasks was very high (Shapes task: μ=96%, SD=3%; Faces-color task: μ=96%, SD=6%; Faces-valence task: μ=97%, SD=5%). No participant was excluded based on overall poor accuracy (<60%). Two participants did not receive auditory feedback during the task and were excluded from analyses. One participant terminated the study after the shapes task. Participants were removed from analyses when their overall mean RT was 2 SD above or below the overall sample mean RT in order to exclude extremely slow or fast participants. The resulting sample size was 56 for shapes task and 57 for faces-color and faces-valence tasks. Trials below 250ms or 2.5 SD above each participant's mean RT per trial type were removed to exclude extremely slow and fast trials (7.5% of trials for shapes task, 5% for face tasks). Then each participant's mean RT on correct trials was calculated separately for distractor and no distractor trials.

A repeated measures analysis of variance (ANOVA), including two factors (task: shapes, faces-color and faces-valence; trial type: distractor and no distractor) was conducted on mean RTs to establish baseline experimental effects and to compare the three tasks. Distractor cost was calculated for RT on each task (distractor minus no distractor). Bivariate correlations were conducted between the distractor cost on each task and trait anxiety, depression and the composite internalizing score. The magnitude of correlation coefficients was compared using a z-test procedure (Meng, Rosenthal, & Rubin, 1992). In order to assess the unique association between RT distractor cost and trait anxiety/symptoms of depression, partial correlations were conducted, controlling for the depression/anxiety scores respectively.

The analyses were repeated for accuracy. Accuracy was very high across all three tasks and showed little variance. There were no significant differences in accuracy between task or trial type. The accuracy distractor cost (distractor trials accuracy minus no-distractor trials accuracy) on each of the three tasks was not significantly associated with trait anxiety, depression symptoms, or the composite internalizing score.

7.4. RESULTS

The mean trait anxiety score was 33.18 (SD=6.80; range=22-49) and the mean depression symptoms score was 4.34 (SD=3.75, range=0-19). The scores were comparable to community norms: trait anxiety normative scores for males were μ=36.30 (SD=6.80) and females μ=38.10 (SD=6.06) (Spielberger, 1973); depression symptoms normative score was μ=4.68 (SD=4.66) (Angold et al., 1995). There were no significant age or sex differences.

Preliminary analyses compared within-task distractor RT cost (distractor trials minus no-distractor trials) for the two blocks comprising each face task. For the faces-color task, there was no significant difference in the distractor cost when the array comprised all neutral faces compared to all angry faces ($t(50)=0.43$, $p=.67$). Likewise, there was no significant difference in distractor cost on the faces-valence task when the array comprised all red faces versus all

green faces (t(54)=.48, p=.63) or when the distractor was an angry face relative to a neutral face (t(56)=0.46, p=.65). There was also no difference in RT on no-distractor trials when the array comprised of all neutral vs all angry faces (t(50)=1.23, p=.23 for faces-color task, t(54)=.71, p=.48 for faces-valence task). Thus, RTs and distractor cost were calculated collapsing across the two blocks within each face task. For mean RT comparisons between female vs male face arrays, see Table E1.

Participants were significantly slower on distractor compared to no distractor trials (F=(1,53)=164.40, p<.001, η_p^2=.76; 2914.87ms vs. 2547.19ms) with this effect observed for all three tasks (Table 7.1). Overall, participants were significantly slower to perform the faces-color task (3097.73ms) compared to the faces-valence task (2956.86ms, p=.003) and slower on both face tasks relative to the shape task (2138.51ms, p's<.001; F=(1.72, 91.04, Huynh-Feldt correction)=185.68, p<.001, η_p^2=.78). Finally, there was a significant task × trial type interaction (F(2,106)=16.97, p<.001, η_p^2=.24). To tease apart this interaction, the distractor costs were entered into a repeated measures ANOVA with Task as the within participant variable. The effect of Task was significant (F=(1.83, 93.48, Huynh-Feldt correction)=11.17, p<.001, η_p^2=.18) with a smaller distractor cost for the faces-valence task compared to the faces-color (p=.01) and shape task (p<.001) but no significant difference between the faces-color and shape task (p=1.00), suggesting that color was more distracting than valence (Figure 7.2).

Trait anxiety and the composite internalizing score were significantly correlated with the distractor cost for each task (Table 7.2). Depression was significantly correlated with distractor cost for the shape and faces-valence task, but while in the expected direction, it did not reach statistical significance for the faces-color task. The strength of association between distractor cost and trait anxiety, depression and internalizing score was not significantly stronger when the distractor was emotionally valenced compared to a non-emotional color distractor (irrespective of face or shape task, z's=-1.28-.48, p's>.05, see Table 7.2 footnote for all comparisons). Within the faces-valence task, distractor cost due to a neutral distractor was

correlated with symptoms of anxiety (r=.34) and depression (r=.27) to the same extent as distractor cost due to an angry distractor (r=.33 for anxiety, r=.31 for depression, all *p*<.05).

Symptoms of anxiety and depression were highly correlated (*r*=.70, *p*<.001**)** making it problematic to confidently decompose their unique contribution to distractor costs. Partial correlations revealed that neither anxiety nor depression uniquely predicted distractor costs for each task.

The overall mean RT on each task was not significantly correlated with symptoms of anxiety/depression (.15-.26, p=.06-.26), except for a significant correlation between anxiety symptoms and an overall RT on faces-valence task (r=.27, p=.04). Looking at the correlations separately for no-distractor and distractor trials, the correlations between symptoms of anxiety/depression and mean RT on no-distractor trials (which indicate baseline performance) were all non-significant (r=.06-.20, p=.14-.63). The correlations with mean RT on distractor trials were generally significant (r=.21-.35, p=.01-.12). The results suggest that the presence of the distractor produces the RT differences as a function of trait anxiety and depression.

7.5. Discussion

The current study was the first to investigate ACT in middle childhood using an irrelevant singleton paradigm. In line with our hypotheses, poorer attentional control, measured as attentional capture by task-irrelevant non-emotional and emotional distractors, was significantly correlated with trait anxiety and symptoms of depression, directly supporting ACT in a school-age sample. The strength of relationship between attentional capture and internalizing symptoms did not differ significantly for non-emotional and emotional distractors. This finding suggests that heightened symptoms of anxiety and depression in childhood are not only associated with attentional processing biases in the presence of emotional information but also appear to be associated with a general attentional deficit for non-emotional stimuli.

Attentional control theory in childhood

Our finding that trait anxiety and symptoms of depression are associated with enhanced attentional capture by a distractor is consistent with our hypothesis, and with previous research demonstrating poorer attentional control in anxious adults using this paradigm (Esterman et al., 2013; Moran & Moser, 2014; Moser et al., 2012) and with evidence from child populations using other paradigms (Eisenberg et al., 2001; Hughes & Ensor, 2011; Muris et al., 2007). However, the current study extends previous findings in several important and novel ways. First, the irrelevant singleton task is a more precise measure of attention than self-report measures or the more complex tasks employed by previous adult and child studies, such as the Stroop task, which are likely to involve multiple cognitive processes. The current method, used here for the first time in young participants, allows direct measurement of the extent to which bottom-up attentional capture dominated top-down control during the initial allocation of attention. The simplicity of the current task (demonstrated by high accuracy on all task variants) is especially important when testing child participants, whose executive functions are not fully developed (Klenberg, Korkman, & Lahti-Nuuttila, 2001) and for whom any additional processes such as memory, language or response selection might interfere with performance to greater degree than in adults. Of note, we observed a significantly smaller distractor cost using emotional face expressions relative to non-emotional color distractors (shape or face), which is consistent with evidence that color is more salient than facial expression (Wolfe & Horowitz, 2004).

Second, ACT is less often investigated in relation to depression than anxiety, especially in children. Our results suggest that poor attentional control is not unique to anxiety as originally proposed by ACT; instead it is associated with a general internalizing symptomatology. This is in line with transdiagnostic views of anxiety and depression, which argue that many cognitive mechanisms are shared between internalizing disorders (Clark & Beck, 2010; Clark & Watson,

1991; Lester, Mathews, Davison, Burgess, & Yiend, 2011; Zavos, Rijsdijk, Gregory, & Eley, 2010).

Attentional control and attentional biases

Third, this study is the first to extend the irrelevant singleton paradigm to study attentional control in the context of emotional distractors. In line with our hypothesis, we found that attentional capture due to emotional and non-emotional distractors was similarly associated with internalizing symptoms, indicating impaired attentional control of non-emotional and emotional processing in anxiety and depression. This tentatively suggests that attentional control deficits might in part account for some of the cognitive biases observed in anxious and depressed participants on tasks using emotional stimuli. That is, attentional biases on emotional tasks might reflect poor attentional control rather than solely selective processing of emotional (e.g. threat) stimuli. This is consistent with previous studies which found that anxious individuals showed bias towards threat only when their self-reported attentional control was low (Derryberry & Reed, 2002; Lonigan & Vasey, 2009; Peers & Lawrence, 2009; Susa et al., 2012). It suggests that dominant bottom-up attentional system might be a risk factor for maladaptive information-processing in anxiety and depression, in line with dual-processing models (Cisler & Koster, 2010). Furthermore, no difference in distractor cost on the faces-valence task was observed for angry vs. neutral face distractors, and these distractor costs were comparably associated with symptoms of anxiety and depression, suggesting that attentional capture was not specific to negatively valenced distractors.

The association between poor attentional control and elevated symptoms of childhood anxiety and depression indicates attentional training as a potential treatment and prevention target for internalizing problems. Preliminary evidence suggests that attentional control training might be successful at reducing internalizing symptoms (Callinan, Johnson, & Wells, 2014; Roughan & Hadwin, 2011); although the effectiveness of cognitive training approaches is

currently debated (Shipstead, Hicks, & Engle, 2012; Wass, Scerif, & Johnson, 2012). Importantly for targeting childhood mental health problems, younger participants seem to benefit more from cognitive training than adults (Wass et al., 2012), possibly reflecting greater neural and behavioral plasticity earlier in development. Finally, future research should explore whether established therapies such as CBT, as well as novel approaches such as attentional-bias modification training (ABM) (Hakamata et al., 2010), improve overall attentional control. This could provide novel insight into the mechanisms of action underpinning these therapeutic processes (Cisler & Koster, 2010).

Limitations

The use of a sensitive behavioral task and its novel adaptation to investigate the role of ACT in the context of emotional stimuli are considerable strengths of the current study. However, there are a number of limitations. First, the sample size was underpowered to investigate sex differences or detect small effects. In addition, we did not detect statistically significant differences in the magnitudes of the correlations between internalizing symptoms and the distractor costs due to non-emotional and emotional distractors. Effect sizes were similar for each of these comparisons. Overall, the results should be replicated in a larger sample. Second, although the relatively narrow age-range allows closer understanding of a specific developmental stage, it limits the generalizability of the results to other ages. ACT needs to be investigated longitudinally to clarify age-related changes in attentional control and its associations with internalizing symptoms across development. Third, in order to replicate the adult study as closely as possible, the shapes task was always completed before the face tasks, thus the carryover effects of the shapes task on the face tasks are not accounted for. However, the faces-color and faces-valence task were fully counterbalanced and therefore performance on these tasks can be compared. Finally, future studies should explore whether the use of different emotional valences in face stimuli may constitute another approach to disentangle attentional bias from attentional control, and possibly uncover disorder-specific cognitive

processes. For example, in addition to using angry face stimuli, it would be interesting to study whether sad face stimuli are equally distracting in depression and anxiety, or whether distractor costs related to sadness are more specific to depression than to anxiety symptoms. Furthermore, it should be tested whether distraction caused by sad faces may be greater than distraction by angry and neutral faces, which would indicate higher attentional bias to sadness as compared to attentional control. Similarly, attentional control in the context of other emotions warrants further exploration.

Conclusions

In conclusion, the current study applied and extended the irrelevant singleton method in order to investigate the relationship between attentional control for both non-emotional and emotional stimuli and symptoms of anxiety and depression in school-aged children. The results demonstrated that childhood symptoms of anxiety and depression are associated with poorer attentional control, supporting ACT in a school-age population. This general attentional deficit might characterize children with elevated symptoms of anxiety and depression and may work alongside or even underpin attentional biases, which are often observed on tasks investigating selective processing of emotional stimuli in this population. Future research should investigate whether attentional control may play a role in the etiology and maintenance of cognitive biases and explore the therapeutic potential of attentional training approaches for anxiety and depression.

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7.7. REFERENCES

AACAP. (2007a). Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 46*(2).

AACAP. (2007b). Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 46*(11).

Angold, A., Costello, E. J., & Erkanli, A. (1999). Comorbidity. *Journal of Child Psychology and Psychiatry, 40*(1), 57-87.

Angold, A., Costello, E. J., Messer, S. C., Pickles, A., Winder, F., & Silver, D. (1995). The development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. *International Journal of Methods in Psychiatric Research, 5*, 1-12.

Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M. J., & van Ijzendoorn, M. H. (2007). Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. *Psychological Bulletin, 133*(1), 1-24.

Callinan, S., Johnson, D., & Wells, A. (2014). A randomised controlled study of the effects of the attention training technique on traumatic stress symptoms, emotional attention set shifting and flexibility. *Cognitive Therapy and Research*, 1-10.

Castaneda, A. E., Tuulio-Henriksson, A., Marttunen, M., Suvisaari, J., & Lönnqvist, J. (2008). A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. *Journal of Affective Disorders, 106*(1), 1-27.

Cisler, J. M., & Koster, E. H. (2010). Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clinical psychology review, 30*(2), 203-216.

Clark, D. A., & Beck, A. T. (2010). Cognitive theory and therapy of anxiety and depression: convergence with neurobiological findings. *Trends in cognitive sciences, 14*(9), 418-424.

Clark, L. A., & Watson, D. (1991). Tripartite model of anxiety and depression: Psychometric evidence and taxonomic implications. *J Adnorm Psychol, 100*, 316-336.

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature reviews neuroscience, 3*(3), 201-215.

Costello, E. J., Mustillo, S., Erkanli, A., Keeler, G., & Angold, A. (2003). Prevalence and development of psychiatric disorders in childhood and adolescence. *Archives of General Psychiatry, 60*(8), 837-844.

Derakshan, N., & Eysenck, M. W. (2009). Anxiety, processing efficiency, and cognitive performance. *European Psychologist, 14*(2), 168-176.

Derryberry, D., & Reed, M. A. (2002). Anxiety-Related Attentional Biases and Their Regulation by Attentional Control. *Journal of Abnormal Psychology, 111*(2), 225-236.

Eisenberg, N., Cumberland, A., Spinrad, T. L., Fabes, R. A., Shepard, S. A., Reiser, M., . . . Guthrie, I. K. (2001). The relations of regulation and emotionality to children's externalizing and internalizing problem behavior. *Child Development, 72*(4), 1112-1134.

Esterman, M., DeGutis, J., Mercado, R., Rosenblatt, A., Vasterling, J. J., Milberg, W., & McGlinchey, R. (2013). Stress-related psychological symptoms are associated with increased attentional capture by visually salient distractors. *Journal of the International Neuropsychological Society, 19*(07), 835-840.

Eysenck, M. W., & Derakshan, N. (2011). New perspectives in attentional control theory. *Personality and Individual Differences, 50*(7), 955-960.

Eysenck, M. W., Derakshan, N., Santos, R., & Calvo, M. G. (2007). Anxiety and cognitive performance: attentional control theory. *Emotion, 7*(2), 336-353.

Finch Jr, A., Montgomery, L., & Deardorff, P. (1974). Reliability of state-trait anxiety with emotionally disturbed children. *Journal of Abnormal Child Psychology, 2*(1), 67-69.

Gregory, A. M., Caspi, A., Moffitt, T. E., Koenen, K., Eley, T. C., & Poulton, R. (2007). Juvenile mental health histories of adults with anxiety disorders. *American Journal of Psychiatry, 164*(2), 301-308.

Hakamata, Y., Lissek, S., Bar-Haim, Y., Britton, J. C., Fox, N. A., Leibenluft, E., . . . Pine, D. S. (2010). Attention bias modification treatment: a meta-analysis toward the establishment of novel treatment for anxiety. *Biological Psychiatry, 68*(11), 982-990.

Hickey, C., McDonald, J. J., & Theeuwes, J. (2006). Electrophysiological evidence of the capture of visual attention. *Journal of Cognitive Neuroscience, 18*(4), 604-613.

Hughes, C., & Ensor, R. (2011). Individual differences in growth in executive function across the transition to school predict externalizing and internalizing behaviors and self-perceived academic success at 6 years of age. *Journal of Experimental Child Psychology, 108*(3), 663-676.

Jacobs, R. H., Reinecke, M. A., Gollan, J. K., & Kane, P. (2008). Empirical evidence of cognitive vulnerability for depression among children and adolescents: A cognitive science and developmental perspective. *Clinical Psychology Review, 28*(5), 759-782.

Joormann, J., & Gotlib, I. H. (2010). Emotion regulation in depression: relation to cognitive inhibition. *Cognition and Emotion, 24*(2), 281-298.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*(6), 593-602.

Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*(6), 617-627.

Klenberg, L., Korkman, M., & Lahti-Nuuttila, P. (2001). Differential development of attention and executive functions in 3-to 12-year-old Finnish children. *Developmental Neuropsychology, 20*(1), 407-428.

Lester, K. J., Mathews, A., Davison, P. S., Burgess, J. L., & Yiend, J. (2011). Modifying cognitive errors promotes cognitive well being: A new approach to bias modification. *Journal of Behavior Therapy and Experimental Psychiatry, 42*(3), 298-308.

Lonigan, C. J., & Vasey, M. W. (2009). Negative affectivity, effortful control, and attention to threat-relevant stimuli. *Journal of Abnormal Child Psychology, 37*(3), 387-399.

Mathews, A., & MacLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annu. Rev. Clin. Psychol., 1*, 167-195.

Meng, X.-L., Rosenthal, R., & Rubin, D. B. (1992). Comparing correlated correlation coefficients. *Psychological Bulletin, 111*(1), 172-175.

Moran, T. P., & Moser, J. S. (2014). The color of anxiety: Neurobehavioral evidence for distraction by perceptually salient stimuli in anxiety. *Cognitive, Affective, & Behavioral Neuroscience*, 1-11.

Moser, J. S., Becker, M. W., & Moran, T. P. (2012). Enhanced attentional capture in trait anxiety. *Emotion, 12*(2), 213-216.

Muris, P., & Field, A. P. (2008). Distorted cognition and pathological anxiety in children and adolescents. *Cognition & Emotion, 22*(3), 395-421.

Muris, P., Meesters, C., & Rompelberg, L. (2007). Attention control in middle childhood: Relations to psychopathological symptoms and threat perception distortions. *Behaviour Research and Therapy, 45*(5), 997-1010.

Muris, P., van der Pennen, E., Sigmond, R., & Mayer, B. (2008). Symptoms of anxiety, depression, and aggression in non-clinical children: Relationships with self-report and performance-based measures of attention and effortful control. *Child Psychiatry and Human Development, 39*(4), 455-467.

Papay, J. P., & Hedl Jr, J. J. (1978). Psychometric characteristics and norms for disadvantaged third and fourth grade children on the State-Trait Anxiety Inventory for Children. *Journal of Abnormal Child Psychology, 6*(1), 115-120.

Peers, P. V., & Lawrence, A. D. (2009). Attentional control of emotional distraction in rapid serial visual presentation. *Emotion, 9*(1), 140-145.

Posner, M. I., & Petersen, S. E. (1990). The attention system of the human brain. *Annual Review of Neuroscience, 13*, 25-42.

Reinholdt-Dunne, M. L., Mogg, K., & Bradley, B. P. (2009). Effects of anxiety and attention control on processing pictorial and linguistic emotional information. *Behaviour Research and Therapy, 47*(5), 410-417.

Roughan, L., & Hadwin, J. A. (2011). The impact of working memory training in young people with social, emotional and behavioural difficulties. *Learning and Individual Differences, 21*(6), 759-764.

Rutter, M., Kim-Cohen, J., & Maughan, B. (2006). Continuities and discontinuities in psychopathology between childhood and adult life. *Journal of Child Psychology and Psychiatry, 47*, 276-295.

Salemink, E., & Wiers, R. W. (2012). Adolescent threat-related interpretive bias and its modification: The moderating role of regulatory control. *Behaviour Research and Therapy, 50*(1), 40-46.

Scott, A., Pearce, D., & Goldblatt, P. (2001). The sizes and characteristics of the minority ethnic populations of Great Britain-latest estimates. *Population Trends, 105*, 6-15.

Shipstead, Z., Hicks, K. L., & Engle, R. W. (2012). Cogmed working memory training: Does the evidence support the claims? *Journal of Applied Research in Memory and Cognition, 1*(3), 185-193.

Snyder, H. R. (2013). Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: A meta-analysis and review. *Psychological Bulletin, 139*(1), 81-132.

Spielberger, C. (1973). *Preliminary test manual for the State-Trait Anxiety Inventory for Children*. Palo Alto: Consulting Psychologists Press, Inc.

Susa, G., Pitică, I., Benga, O., & Miclea, M. (2012). The self regulatory effect of attentional control in modulating the relationship between attentional biases toward threat and anxiety symptoms in children. *Cognition & emotion, 26*(6), 1069-1083.

Theeuwes, J. (1991). Cross-dimensional perceptual selectivity. *Perception and Psychophysics, 50*(2), 184-193.

Theeuwes, J. (1992). Perceptual selectivity for color and form. *Perception and Psychophysics, 51*(6), 599-606.

Theeuwes, J. (2010). Top–down and bottom–up control of visual selection. *Acta Psychologica, 135*(2), 77-99.

Tottenham, N., Tanaka, J. W., Leon, A. C., McCarry, T., Nurse, M., Hare, T. A., . . . Nelson, C. (2009). The NimStim set of facial expressions: judgments from untrained research participants. *Psychiatry Research, 168*(3), 242-249.

Wass, S., Scerif, G., & Johnson, M. H. (2012). Training attentional control and working memory–Is younger, better? *Developmental Review, 32*(4), 360-387.

Wolfe, J. M., & Horowitz, T. S. (2004). What attributes guide the deployment of visual attention and how do they do it? *Nature reviews neuroscience, 5*(6), 495-501.

Zavos, H., Rijsdijk, F. V., Gregory, A. M., & Eley, T. C. (2010). Genetic influences on the cognitive biases associated with anxiety and depression symptoms in adolescents. *Journal of Affective Disorders, 124*(1), 45-53.

Figure 7.1 - Example of no-distractor and distractor trials for each of the three tasks used in the study: a) Shapes task, b) Faces-color task, c) Faces-valence task

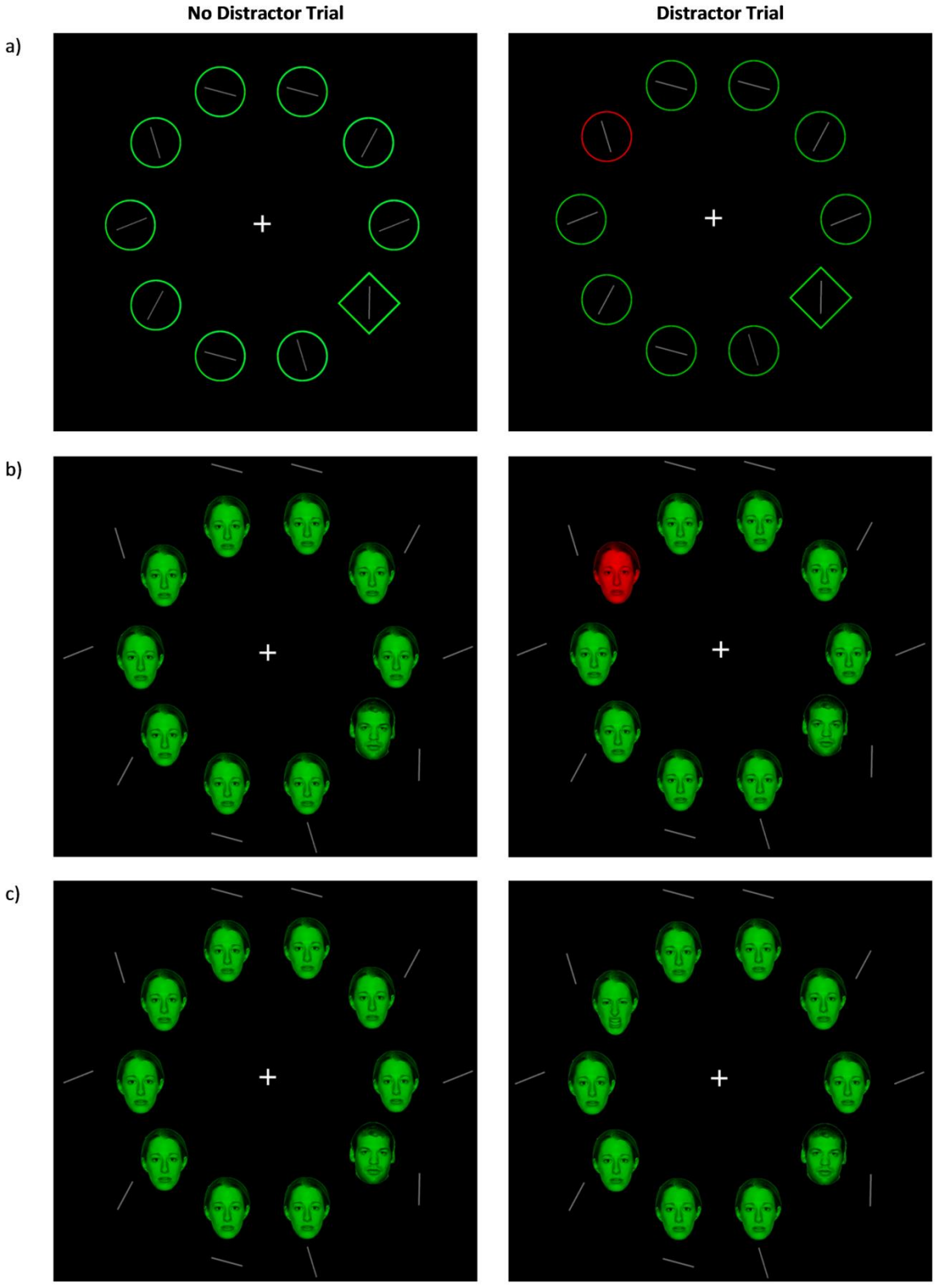


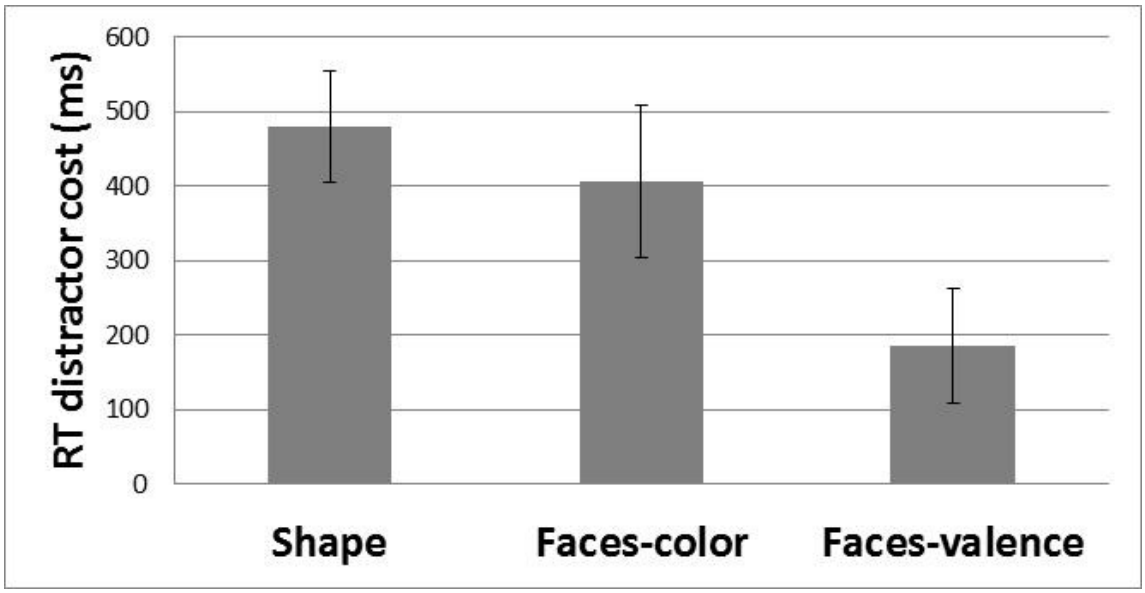
Figure 7.1 (continued). Example of no-distractor and distractor trials for each of the three tasks used in the study: a) Shapes task, b) Faces-color task, c) Faces-valence task

Notes:

In shapes task example, on both trials a diamond is a target shape and participants are required to indicate by button press that the line inside is vertical. On a distractor trial one of the circles in the array is of a task-irrelevant distractor of opposite color (red/paler gray).

In faces-color and faces-valence tasks examples, a male face is a target face and participants are required to indicate by button press that the line next to it is vertical. In faces-color task example on a distractor trial one of the female faces in the array is of a task-irrelevant distractor of opposite color (red/darker gray). In faces-valence task example on a distractor trial one of the female faces in the array is of a task-irrelevant distractor of opposite valence (an angry facial expression).

Figure 7.2 - RT distractor cost for the shapes, faces-color and faces-valence tasks



Notes:

Error bars indicate 95% confidence intervals. Non-overlapping confidence intervals indicate significant difference between the mean scores.

Table 7.1 - RT on distractor and no-distractor trials, and RT distractor cost for each task, and each block within faces tasks

Task	*N*	*RT Distractor (ms)* Mean (SD)	*RT No distractor (ms)* Mean (SD)	*Distractor Cost (ms)* Mean (SD)
Shape (all trials)	**56**	**2391.24 (537.34)**	**1911.25 (392.20)**	**479.99 (285.89)**
Faces-color (all trials)	**57**	**3349.43 (701.23)**	**2944.04 (693.59)**	**405.39 (392.86)**
Neutral face array, red/green distractor	*55*	3378.12 (709.50)	2926.22 (584.92)	451.90 (501.36)
Angry face array, red/green distractor	*53*	3267.47 (735.95)	2863.13 (736.42)	404.34 (456.45)
Faces-valence (all trials)[a]	**57**	**3075.44 (634.44)**	**2889.84 (584.78)**	**185.60 (299.46)**
Green face array, angry/neutral distractor	*57*	3142.82 (726.40)	2942.46 (673.47)	200.36 (372.46)
Red face array, angry/neutral distractor	*55*	3035.44 (659.99)	2842.45 (586.80)	192.99 (367.69)

Notes:

[a] Faces-valence distractor trials can also be divided into:

Angry face array, neutral face distractor cost =170.75 (448.80) (relative to mean faces-valence no distractor RT)

Neutral face array, angry face distractor cost = 200.45 (313.08) (relative to mean faces-valence no distractor RT)

Table 7.2 - The correlation between RT distractor cost for each task, and trait anxiety, depression symptoms and composite internalizing score.

Task distractor cost	Trait Anxiety	Depression Symptoms	Composite Internalizing
Shapes	.27*	.30*	.31*
Faces-color	.26*	.16	.23
Faces-valence	.40*	.38*	.43*

Notes:

* is $p < .05$

The correlations were not significantly different:

Correlations with trait anxiety: Faces-color vs. Faces-valence: r=.26 vs .40, z=-.84, p=.20; Shapes vs. Faces-valence: r=.27 vs .40, z=-.78, p=.22; Faces-color vs. Shapes: r=.26 vs .27, z=-.06, p=.47

Correlations with depression: Faces-color vs. Faces-valence: r=.16 vs .38, z=-1.28, p=.10; Shapes vs. Faces-valence: r=.30 vs .38, z=-.48, p=.32; Faces-color vs. Shapes: r=.16 vs .30, z=-.88, p=.19

Correlations with composite internalizing: Faces-color vs. Faces-valence: r= .23 vs .43, z=-1.20, p=.12; Shapes vs. Faces-valence: r=.31 vs .43, z=-.73, p=.23; Faces-color vs. Shapes: r=.23 vs .32, z=-.51, p=.30.

8. DISCUSSION

8.1. OVERVIEW

This chapter provides an overview of the findings of the current thesis. First, results from each empirical chapter are outlined. Second, results are interpreted in the context of existing research and theoretical and clinical implications of the findings are discussed. Next, future directions are proposed, followed by limitations of the current thesis. Finally, concluding remarks are made.

8.2. RESULTS SUMMARY

The current thesis used both phenotypic and genetic analyses to study two broad aims. First, analyses explored genetic and environmental influences on anxiety, depression and their co-occurrence across development. Second, the thesis investigated three cognitive processes involved in child and adolescent depression and anxiety: anxiety sensitivity, mindfulness and attentional control. Key results of each empirical chapter are outlined in this section.

The first two empirical chapters used twin modelling methodology to investigate developmental associations between depression and four different anxiety symptom clusters. *Chapter 3* examined the phenotypic and genetic structure of these symptoms in childhood, adolescence and young adulthood. Looking at the phenotypic correlations, when controlling for other anxiety subscales, depression symptoms in childhood were only associated with generalized anxiety symptoms; this association broadened to panic and social phobia symptoms in adolescence; and to all anxiety subscales in young adulthood. Twin modelling

results were in line with phenotypic results. In childhood, anxiety subscales were influenced by a single genetic factor that did not contribute to genetic variance in depression symptoms, suggesting largely independent latent genetic influences on anxiety and depression. In adolescence, genetic influences were significantly shared between depression and all anxiety subscales. In young adulthood, a genetic internalizing factor influencing depression and all anxiety subscales emerged, alongside a small significant genetic fear factor.

Chapter 4 followed up the cross-sectional analyses using a longitudinal design and focused on continuity and change of genetic and environmental influences on depression, anxiety symptoms and their co-occurrence across adolescence and young adulthood. Phenotypic analyses found that each depression and anxiety symptom scale was moderately stable and that they correlated with one another over time. The phenotypic continuity of each symptom was largely underpinned by genetic stability, but new genetic influences contributing to change in the developmental course of symptoms emerged at each time point. Latent genetic influences, both stable and time-specific, overlapped considerably between the scales. Conversely, non-shared environmental influences were largely time- and symptom-specific, although some contributed moderately to the stability of depression and anxiety symptom scales. These stable, longitudinal environmental influences were highly correlated between the symptom scales.

The remaining three empirical chapters investigated cognitive processes involved in the aetiology and maintenance of depression and anxiety. *Chapter 5* used twin modelling methodology to investigate phenotypic and genetic associations between anxiety sensitivity dimensions and depression and anxiety symptoms cross-sectionally across childhood, adolescence and young adulthood. When controlling for all other concurrent associations, phenotypic analyses revealed that physical concerns were uniquely associated with anxiety, but not depression, at all ages. Social concerns were uniquely associated with depression in adolescence, while mental concerns were more strongly associated with depression than with

anxiety. Genetic results mirrored the pattern of phenotypic associations – genetic influences on physical concerns overlapped substantially more with anxiety than depression, while genetic influences on mental and social concerns were shared to a similar extent with both depression and anxiety.

Chapter 6 continued to investigate the association between depression and anxiety sensitivity, as well as explored associations between depression, anxiety sensitivity and mindfulness. The analyses focused on attentional control aspect of trait mindfulness, given the established association between low attention control and internalising symptoms. This study was the first to investigate the quantitative genetics of mindfulness, and found that this trait is moderately heritable, with the remaining variance accounted for by non-shared environmental influences, with no significant influence of shared environment. All three variables were moderately associated with each other, and these phenotypic correlations were underpinned largely by latent shared genetic influences. Environmental influences were mostly symptom-specific.

Finally, *chapter 7* investigated the question of disorder-specific versus shared cognitive processes in depression and anxiety using an experimental design. It focused on attentional control abilities in middle childhood, measured using a visual search task based on the irrelevant singleton paradigm. Attentional capture by task-irrelevant non-emotional (colour) and emotional (facial expressions) distractors was measured. Significant attentional capture by both non-emotional and emotional distractors was observed, and the amount of capture was significantly correlated with trait anxiety and symptoms of depression. The strength of relationship between attentional capture and the symptoms did not differ significantly for non-emotional and emotional distractors, indicating a similar degree of impaired attentional control for non-emotional and emotional information. This suggests that attentional deficits might in part account for some of attentional biases often observed in anxious and depressed children on tasks investigating processing of emotional stimuli.

8.3. Results interpretations and implications

8.3.1. Genetic and environmental influences on depression, anxiety and their co-occurrence across development

The current thesis advances the existing literature on developmental changes in the aetiology of internalizing problems in three major ways. First, it comprehensively explores developmental age differences in the higher order genetic structure of internalizing symptoms in the context of different theoretical models. Second, it adds to research investigating the genetic and environmental contributions to homotypic continuity of depression and different anxiety symptom clusters. Finally, results presented in this thesis increase our understanding of the aetiological influences on heterotypic continuity of depression and anxiety symptoms.

Age differences in higher order genetic structure

The results presented in Chapter 3 suggest that the phenotypic associations between depression and different anxiety types might differ across development. In childhood (mean age 8 years), when controlling for concurrent associations, only generalized anxiety symptoms were associated with depression. In adolescence, co-occurrence increased – partial correlations revealed that at mean age 15 years, depression was associated with three anxiety subscales: generalized anxiety, panic and social anxiety symptoms. In young adulthood (mean age 20 years), these associations broadened further with depression symptoms significantly correlating with all anxiety symptom clusters. Thus, the pattern of phenotypic results suggests that there might be more co-occurrence between depression and different anxiety types from adolescence onwards. The finding that depression and generalized anxiety are consistently

associated with each other at all five ages investigated is in line with previous studies that find that these two symptom groups are particularly closely related (Hettema, 2008a; Mennin et al., 2008; Moffitt et al., 2007).

At the etiological level, different higher order genetic structures of internalizing symptoms were observed at three developmental phases, with common genetic vulnerability across depression and anxiety symptoms only emerging in adolescence. In childhood, a genetic factor common to all anxiety types did not influence depression symptoms, suggesting largely separate aetiology of childhood depression and anxiety. This is in contrast to one previous study that has found genetic overlap between general distress and different anxiety types in pre-school children (Eley et al., 2003), however the general distress scale included generalized anxiety symptoms in addition to depression symptoms, which may have accounted for the genetic overlap. In adolescence, no higher order genetic structure emerged. Instead, the etiological structure reflected the DSM-5 conceptualization of distinct but correlated disorders. The high genetic overlap between depression and anxiety symptom clusters is in line with other studies that looked at the shared aetiology of internalizing symptoms in this age group (Eley et al., 2003; Eley & Stevenson, 1999; Lahey et al., 2011; Nelson et al., 2000; Thapar & McGuffin, 1997; Zavos, Rijsdijk, et al., 2012). However, results observed both in childhood and adolescence are in contrast to other studies that investigated the genetic overlap between different internalizing problems in young people and found support for a single genetic factor influencing a range of internalizing symptoms (Cosgrove et al., 2011; Lahey et al., 2011; Silberg & Bulik, 2005; Silberg et al., 2001).

One reason for the discrepancy might be that the previous studies encompass broad age-ranges spanning childhood and adolescence, thus cannot capture age-specific changes in the shared aetiology of depression and anxiety. These age differences may be relevant given that anxiety emerges in childhood while the prevalence of depression increases markedly in adolescence (Ford et al., 2003; Kessler, Berglund, et al., 2005) and in the context of previous

findings that depression pre and post adolescence may differ substantially (Rutter et al., 2006). Specifically, childhood-onset depression does not predict adolescent or adult depression (Harrington, Rutter, & Fombonne, 1996) and sex differences in prevalence rates emerge post adolescence (Moffitt et al., 2007). Furthermore, childhood-onset depression is characterised by more severe psychosocial risks, such as higher rates of perinatal insults, motor skill deficits, caretakers instability and psychopathology, than adult-onset depression (Jaffee et al., 2002; Korczak & Goldstein, 2009). Taken together, this suggests that depression pre and post adolescence might be characterised by separate aetiology and this might explain why genetic overlap with anxiety is not observed in the child sample.

In young adulthood, two genetic factors emerged, one loading on all internalizing symptoms and the other influencing the fear disorders, although the genetic fear factor had a relatively small influence on the fear symptoms. Thus, the genetic analyses provided support for both unidimensional (Eaton et al., 2011; Fergusson et al., 2006; Krueger, Caspi, et al., 1998; Seeley et al., 2011) and bidimensional (distress and fear) (Eaton et al., 2013; Sellbom et al., 2008; Slade & Watson, 2006; Vollebergh et al., 2001; Watson, 2005) conceptualizations of internalizing psychopathology in young adulthood. The analyses are in agreement with a growing literature from adult populations supporting a single internalizing genetic factor on depression and anxiety (Goes et al., 2012; Kendler, Aggen, et al., 2011; Mosing et al., 2009). In addition, the genetic fear factor is in line with one study that found separate genetic influences on the distress (depression and generalized anxiety) and fear (animal and situational phobias) symptoms, with both genetic factors loading on panic symptoms (Kendler, Prescott, et al., 2003).

Taken together, results from Chapter 3 suggest that the phenotypic and genetic structure of internalizing symptoms may differ across development. Depression and anxiety seem to be somewhat distinct in childhood, but become more associated and share most of their genetic aetiology from adolescence, with an overarching internalizing genetic factor emerging in early

adulthood. High genetic correlations between phenotypes are often interpreted as an indication that the same genes affect the phenotypes. The current results are in line with the generalist genes hypothesis and provide evidence for *pleiotropy* – whereby genes affect multiple different traits simultaneously. However, the difference in genetic results pre- and post-adolescence suggests that some genetic influences may be important only at one developmental stage. Overall, this pattern of results suggests that the aetiology of the relationship between depression and anxiety is dynamic and provided the rationale for using longitudinal models in Chapter 4.

Homotypic continuity

Chapter 4 focused firstly on aetiological influences underpinning homotypic and heterotypic continuity of depression and anxiety symptoms across adolescence and young adulthood. Depression was found to be moderately stable across this developmental period (r=.38-.47). This finding is in line with previous studies that have found that depression is characterised by moderate homotypic stability in adulthood (Lahey et al., 2014), and that adolescent depression continues to adulthood (Dunn & Goodyer, 2006; Harrington et al., 1990). Focusing on aetiological influences underpinning this phenotypic stability, results in Chapter 4 suggest that the continuity of depression is largely due to genetic stability, with latent genetic influences at 15 years continuing to influence depression symptoms at ages 17 and 20. This is in line with other twin studies that find support for genetic stability in depression across development as well as in adulthood (Bolhuis et al., 2014; Gillespie et al., 2004; Lau & Eley, 2006; Nivard et al., 2014; Tully et al., 2010), suggesting that genes may be one of the important reasons for the chronic nature of depression. However, unlike in one developmental study (Scourfield et al., 2003), shared environmental influences were not significant and did not contribute to stability of depression. This might be because the current sample was older and shared environmental influences on depression are thought to decrease with age (Bergen et al., 2007; Rice et al., 2002a). In addition to genetic stability, new genetic influences were found to emerge over

time and contribute to the change in symptoms. A similar pattern of genetic innovation and attenuation has been demonstrated in three previous studies (Lau & Eley, 2006; Nivard et al., 2014; Scourfield et al., 2003). Finally, non-shared environmental influences were largely (but not entirely) time-specific and tended to contribute to the change of depression symptoms over time, which once again is in line with a majority of longitudinal twin studies in depression. Taken together, these results support the growing empirical evidence that genetic influences on depression change dynamically across development.

Moving on to homotypic continuity of anxiety, each anxiety scale was moderately stable over adolescence and young adulthood (r=.35-.58), with no significant differences between the stability of different anxiety types. This is in line with previous evidence of moderate stability of different anxiety types in adults (Lahey et al., 2014), and considerable continuity of anxiety from adolescence to adulthood (Bittner et al., 2007; Gregory et al., 2007; Pine et al., 1998). The results in Chapter 4 suggest that, similarly to depression, continuity of each of anxiety symptoms is largely underpinned by genetic stability, but there was also evidence for genetic innovation and attenuation. Non-shared environmental influences were largely time-specific, with very small (but generally significant) contribution to the stability of anxiety symptoms. These results are in line with previous studies, but the use of four different anxiety types in Chapter 4 also significantly extends the existing research. To date the contribution of genetic and environmental influences to homotypic continuity of anxiety has mostly been explored for total anxiety score or fears/phobias, and these studies generally find genetic stability (Garcia et al., 2013; Gillespie et al., 2004; Kendler, Gardner, Annas, et al., 2008; Lewis & Plomin, 2015; Nivard et al., 2014; Trzaskowski et al., 2011; Waszczuk et al., 2013; Zavos, Rijsdijk, et al., 2012). Three twin studies have also found genetic innovation and attenuation (Kendler, Gardner, Annas, et al., 2008; Lewis & Plomin, 2015; Trzaskowski et al., 2011).

Only one study has looked specifically at aetiological underpinnings of the continuity of different anxiety types investigated in Chapter 4. Homotypic continuity of panic, separation

and generalized anxiety symptoms was characterized by stable genetic influences across middle childhood (Waszczuk et al., 2013). The results in Chapter 4 extend these analyses to adolescence and young adulthood, as well as providing novel evidence about the aetiology of homotypic stability of social anxiety. Unlike in childhood, continuity of these anxiety types is characterised by both genetic stability and genetic innovation across adolescence and young adulthood. Finally, results extend the existing research by indicating some notable differences between different anxiety types: generalized and social anxiety symptoms showed somewhat more genetic stability than panic and separation anxiety symptoms, where genetic influences tended to attenuate more sharply, with proportionately greater genetic innovation at age 17 (panic and separation anxiety symptoms) and 20 years (separation anxiety symptoms). This might reflect relatively late median age of onset of panic disorder (Costello et al., 2003; Kessler, Berglund, et al., 2005), and that paediatric and adult-onset separation anxiety might differ considerably (Costello, Copeland, & Angold, 2011; Shear, Jin, Ruscio, Walters, & Kessler, 2006).

Heterotypic continuity

Heterotypic continuity across different internalizing symptoms was moderate, both between depression and anxiety (r=.11-.39), as well as among different anxiety types (r=.16-.46). This longitudinal comorbidity was largely explained by genetic overlap between stable genetic influences that contribute to chronicity of each symptom, as well as overlap between time-specific genetic influences. Time-specific influences represent developmentally dynamic genes that operate across short time periods and might reflect the innovation genes that come online in late adolescence or young adulthood. The results in Chapter 4 provide preliminary evidence that both stable and time-specific latent genetic influences have general effects on both depression and different anxiety types, contributing to the enduring high genetic overlap between different internalizing symptoms over time. Conversely, latent environmental influences were largely time- and symptom-specific, thus contributing to *change* in

comorbidity over time. However, a modest proportion of environmental influences contributed significantly to the stability of each symptom scale, albeit to a lesser extent than genetic influences.

The role of stable shared genetic influences is in line with a small number of studies that have investigated the quantitative genetics of heterotypic continuity between depression and different anxiety types and found that it is mostly genes that underpin this association over time. One study found that the heterotypic continuity between overanxious disorder, separation anxiety and specific phobia in childhood and adolescence was driven by genetic and shared environmental influences, and that common genetic influences on childhood overanxious disorder and phobias continue to adolescence, where they also predict variance in adolescent depression (Silberg et al., 2001). Following up on this in the same sample, a second study found that a single set of genetic influences loaded on depression, overanxious disorder, separation anxiety and eating disorder symptoms measured first in childhood and then in adolescence (Silberg & Bulik, 2005). Furthermore, another study found, in a sample of young people aged 5-17 at baseline, that early anxiety symptoms and later depression symptoms were associated due to a shared genetic risk factor (Rice et al., 2004). Finally, genetic influences on childhood separation anxiety disorder have been found to continue to influence adult onset panic attacks (Roberson-Nay et al., 2012). Taken together these studies are in line with Chapter 4 results that genetic stability of shared genes largely underpins heterotypic continuity of different internalizing symptoms. Importantly, the current results extend these genetic findings to the novel age range of adolescence and young adulthood, and to novel anxiety types such as generalized and social anxiety, showing that this developmental pattern of shared aetiological influences is broad rather than specific to certain pairs of disorders. Furthermore, the model used in Chapter 4 allowed us to investigate the overlap between stable and time-specific latent genetic influences, showing that the genetic overlap between

depression and anxiety occurs both at the level of genetic stability as well as genetic innovation.

Finally, non-shared environmental results are also noteworthy, as this is the first demonstration that stable non-shared environmental influences overlap considerably between depression and anxiety symptom scales, contributing to the co-occurrence of depression and different anxiety types over time. These stable environmental influences may produce enduring effects though biological and social changes in an individual (Kendler, Eaves, et al., 2011), and seem to act in a largely transdiagnostic manner. These environmental influences may include effects of severe environmental stressors such as childhood maltreatment or natural disasters (Anda et al., 2006; Asselmann et al., 2015; Goenjian et al., 2005; Kendler et al., 2000).

8.3.2. Cognitive biases and cognitive control in depression and anxiety in young people

The current thesis advances the existing literature on cognitive biases and cognitive control in depression and anxiety in three major ways. First, the results increment the existing research on cognitive biases and cognitive control in depression and anxiety by studying these processes together, using both genetically informative and experimental approaches. Second, the phenotypic and genetic specificity in associations between cognitive biases, depression and anxiety was explored, providing novel evidence for both shared and symptom-specific cognitive processes and contents in internalizing symptoms in young people. Third, the results provide novel evidence about the shared aetiology of cognition and internalizing symptoms.

Relationship between cognitive biases and cognitive control

Chapters 5, 6 and 7 explored the relationship between cognitive biases, cognitive control deficits and internalizing problems. First, chapter 5 and 6 provided novel evidence that internalizing symptoms were consistently associated with anxiety sensitivity in childhood, adolescence and young adulthood, as expected based on the large literature in this area (Naragon-Gainey, 2010; Olatunji & Wolitzky-Taylor, 2009). Chapter 7 has also found significant attentional biases in childhood anxiety and depression using a novel visual search task, which also confirms previous studies that used other methodologies (Bar-Haim et al., 2007; Joormann et al., 2007; Kyte et al., 2005). Finally, in chapter 7, depression symptoms and trait anxiety were associated with poorer performance on attentional control tasks, in line with previous research demonstrating poorer attentional control in anxious adults using an irrelevant singleton paradigm (Esterman et al., 2013; Moran & Moser, 2014; Moser et al., 2012) and with evidence from child populations using other paradigms (Eisenberg et al., 2001; Hughes & Ensor, 2011; Muris et al., 2007). However, cognitive control results extend previous findings in several important ways. First, the irrelevant singleton task is considered a more precise measure of attention than self-report measures or the more complex tasks employed by previous adult and child studies, such as the Stroop task, which are likely to involve multiple cognitive processes. The irrelevant singleton method, used here for the first time in young participants, allows direct measurement of the extent to which bottom-up attentional capture dominated top-down control during the initial allocation of attention. The simplicity of the task (demonstrated by high accuracy on all task variants) is especially important when testing child participants, whose executive functions are not fully developed (Klenberg, Korkman, & Lahti-Nuuttila, 2001) and for whom any additional processes such as memory, language or response selection might interfere with performance to a greater degree than in adults. Finally, the finding in chapter 6 that depression is characterized by lower levels of mindfulness is also in line with previous studies (Brown & Ryan, 2003; Cash & Whittingham, 2010), and adds to the

evidence for poor cognitive control in internalizing symptoms. Taken together, the results from chapters 5, 6 and 7 support the view that internalizing symptoms in young people are characterised both by impaired cognitive control and by cognitive biases.

The relationship between cognitive biases and cognitive deficits was explored in chapters 6 and 7. First, in chapter 6, a moderate association was found between adolescent anxiety sensitivity and low levels of mindfulness (specifically the awareness of the present moment experience). This association is in line with evidence from previous studies in adult samples (McCracken & Keogh, 2009; Vujanovic et al., 2007). The research in adults suggests that anxiety sensitivity might be underpinned by low levels of cognitive control, which results in a range of processes that maintain anxiety sensitivity and contribute to distress, such as experiential avoidance, poor interoceptive exposure and reduced bodily awareness in a self-compassionate manner. Given the significant link between anxiety sensitivity and mindfulness in adolescence, these processes might also be relevant in younger people. Furthermore, the analyses in chapter 6 were able to extend the existing research into a new direction by providing initial evidence that the association between anxiety sensitivity and mindfulness is underpinned by a considerable degree of genetic and non-shared environmental overlap. It remains unclear what specific genetic and environmental influences might underpin this association (for more discussion see below).

Analyses in chapter 7 investigated whether attentional control was similarly impaired in the context of non-emotional and emotional distractors in children with elevated depression and anxiety symptoms. The results indicated that attentional capture due to emotional and non-emotional distractors was similarly associated with internalizing symptoms. Furthermore, no difference in distractor cost on the emotional version of the visual search task was observed for angry vs. neutral face distractors. These distractor costs were comparably associated with symptoms of anxiety and depression, suggesting that attentional capture was not specific to negatively valenced distractors. Taken together, the results tentatively suggest that attentional

control deficits might in part account for some of the cognitive biases observed in anxious and depressed children on tasks using emotional stimuli. That is, attentional biases on emotional tasks might reflect poor attentional control rather than solely selective processing of emotional (e.g. threat) stimuli. This is consistent with previous studies which found that anxious adults and children showed bias towards threat only when their self-reported attentional control was low (Derryberry & Reed, 2002; Lonigan & Vasey, 2009; Peers & Lawrence, 2009; Susa et al., 2012). It suggests that dominant bottom-up attentional system might be a risk factor for maladaptive information-processing in anxiety and depression, in line with dual-processing models (Cisler & Koster, 2010).

Specificity of cognitive processes and contents

In chapter 7, two cognitive *processes* were investigated in depression and anxiety. Both attentional control in the context of neutral stimuli, and attentional bias in the context of emotional information, measured using analogue visual search tasks, were similarly associated with depression and anxiety symptoms in a sample of primary school children. First, this suggests that impaired attentional processing of non-emotional information is a transdiagnostic cognitive marker of internalizing symptoms. The results are in line with previous research that found that attentional control is impaired in a range of internalizing problems (Beaudreau & O'Hara, 2008; Castaneda et al., 2008; Eysenck & Derakshan, 2011; Hammar & Årdal, 2009; Joormann & Gotlib, 2010; Snyder, 2013). However, the current study is one of the first to directly address the issue of specify of cognitive deficits to different internalizing symptoms. Some previous studies have found that inhibitory deficits are specific to anxiety and not depression (Beaudreau & O'Hara, 2009; Lyche et al., 2011; Thomas et al., 2009). The current results argue instead that cognitive control deficits may be transdiagnostic in childhood. Furthermore, while *attentional control theory* was originally proposed for anxiety (Derakshan & Eysenck, 2009; Eysenck et al., 2007), current results support the view that the theory may also be applicable to depression. Second, the results support previous findings that

attentional cognitive biases are observed both in childhood anxiety and depression (Bar-Haim et al., 2007; Joormann et al., 2007; Kyte et al., 2005). The existing visual search literature is skewed towards investigating attentional biases in anxiety and the current study adds to the existing research by showing that hypervigilance to emotional information in visual search paradigms can also be observed in depression.

The shared and unique cognitive *content* of one maladaptive thought process – anxiety sensitivity – was investigated in chapter 5. The analyses were conducted at five different developmental stages and were the first to comprehensively investigate developmental changes in the relationship between anxiety sensitivity, depression and anxiety. Both phenotypic and genetic results were remarkably consistent across all ages. First, phenotypic analyses showed that the *physical concerns* dimension of anxiety sensitivity was uniquely associated with anxiety but not depression, and shared greater genetic influences with anxiety than depression at all waves. The phenotypic results are in agreement with previous studies that found that the fear of physical sensations might be uniquely associated with anxiety in adults (Hendriks et al., 2014; Taylor et al., 1996) as well as in young people (Brown, Meiser-Stedman, et al., 2014; Dehon et al., 2005; Joiner et al., 2002; Muris, 2002). Twin modelling results are the first to suggest that this phenotypic specificity of physical concerns to anxiety but not depression symptoms might be underpinned by a degree of genetic specificity.

Second, *social concerns* were not specifically associated with anxiety or depression in childhood and adulthood, but were specifically associated with depression symptoms in adolescence. This is in line with some of previous studies which found that social concerns characterise both depression and anxiety (Dehon et al., 2005; Hendriks et al., 2014; McWilliams et al., 2007; Viana & Rabian, 2009). Third, *mental concerns* were independently related to both anxiety and depression symptoms across development, with a tendency for stronger associations with depression than anxiety. This supports a majority of studies that found that mental concerns are present both in depression and anxiety (Brown, Meiser-

Stedman, et al., 2014; Dehon et al., 2005; Hendriks et al., 2014; Noel et al., 2013; Schmidt et al., 1998; Viana & Rabian, 2009; Zinbarg et al., 2001). However, the evidence was found for potential age differences in this association, with a tendency for stronger associations between mental concerns and depression symptoms in adolescence, which may explain why some studies found that mental concerns might be specific to depression or distress disorders (Rector et al., 2007; Rodriguez et al., 2004; Taylor et al., 1996). Genetic and non-shared environmental influences on *social* and *mental concerns* were moderately correlated with both anxiety and depression symptoms at all waves, although genetic correlations tended to be higher than non-shared environmental correlations. This suggests that the relative lack of phenotypic specificity was reflected at the genetic level, with these two anxiety sensitivity subtypes sharing a similar degree of their genetic influences with depression and anxiety.

Overall, these results provide a partial support for the *cognitive content-specificity hypothesis*, which proposes that depression and anxiety share biased cognitive *processes*, but can be differentiated by the *content* of emotional information that elicits the biases (Beck et al., 1987; Beck & Perkins, 2001; Clark & Beck, 1989). Results obtained in chapter 7 support the view that impaired attentional control, as well as attentional biases, might constitute transdiagnostic cognitive processes common to depression and anxiety. Anxiety sensitivity was also found to be a maladaptive cognitive *process* that is important both in depression and anxiety, but three subscales provide information about the differential *content* of anxiety sensitivity. Out of these three subscales, the results in chapter 5 suggest that only physical concerns are uniquely linked to anxiety, and this specificity was found to be underpinned by a degree of genetic specificity, and was observed across different developmental stages. This unique and persistent relationship between anxiety and physical concerns might be because physical concerns are specifically capturing perceived threat or danger to one's life or physical health, which might be particularly salient in anxiety. According to the cognitive content-specificity hypothesis, threat-related cognitions are thought to constitute the core unique content of anxiety

disorders, while depression is characterised by the content of loss and sadness. Conversely, both the social and mental concerns scales showed broad associations with both anxiety and depression, with somewhat stronger associations with depression than anxiety. This indicates that concerns about the loss of cognitive control or about how others perceive an individual's symptoms of anxiety do not constitute unique content for depression or anxiety. This might be because these concerns are broad and do not specifically capture threat or loss content. Thus, they may constitute transdiagnostic concerns instead. Another reason might be that both scales contain only three items each (two for social concerns measured in adulthood), resulting in lower internal consistencies and possibly poor coverage of symptoms. Taken together, the results from chapters 5 and 7 support the view that the cognitive processes involved in depression and anxiety are broad, and also provide evidence that some of the content of these cognitions might be disorder-specific.

Shared aetiology of cognition and internalizing symptoms

The current thesis adds to the growing research on the relative contribution of genetic and environmental influences on cognitive processes relevant in depression and anxiety. First, the results in chapter 5 demonstrate that each subscale of anxiety sensitivity is moderately heritable across development, with the remaining variance explained by non-shared environmental influences. This is in line with previous results (Brown et al., 2012; Stein et al., 1999; Taylor et al., 2008) but extends these conclusions to middle childhood. Of note, one previous study in adults found no genetic influences on the social concerns subscale (Stein et al., 1999), unlike results from the adult group in the current sample. Second, the results in chapter 6 are the first to demonstrate that mindfulness is also moderately heritable in adolescence, with moderate non-shared environmental influences and no shared environmental influences. Interestingly, no sex differences were found in the aetiology of anxiety sensitivity or mindfulness. To date only one study found sex differences in the aetiology of anxiety sensitivity, with genetic influences emerging only in females (Taylor et al.,

2008). In contrast, the current results support the view that the aetiology of these two cognitive phenotypes is comparable across males and females. Finally, the results in chapter 6 indicate that there is a considerable degree of genetic and non-shared environmental overlap between anxiety sensitivity and mindfulness. Taken together, these results suggest that cognitive processes relevant to internalizing symptoms arise both due to genetic predispositions, as well as a result of individual-specific environmental influences. Some of these aetiological influences might be broadly influencing different aspects of cognition, while the remaining proportion of genetic and environmental influences seems to be specific to a given cognitive process.

To date a number of studies have looked at specific genes implicated in the aetiology of cognitive processes relevant to depression and anxiety. Candidate gene studies examining specific genetic influences on cognitive biases provide initial support that the homozygous short allele of the 5-HTTLPR gene is moderately associated with increased maladaptive cognition (Beevers et al., 2011; Beevers et al., 2009; Fox et al., 2009; Pergamin-Hight et al., 2012; Thomason et al., 2010). Focusing specifically on anxiety sensitivity, to date it remains unclear whether carriers of short alleles of this gene experience higher anxiety sensitivity than long allele carriers (Klauke et al., 2011; Stein et al., 2008; Zavos, Wong, et al., 2012). Interestingly, a recent review found that individuals carrying the s variant of the 5-HTTLPR outperform subjects carrying the long allele in a range of cognitive tasks measuring executive functioning, possibly due to increased vigilance (Homberg & Lesch, 2011). Several other genes linked to serotonin and dopamine neurotransmitters have been implicated in cognitive control (Barnett, Jones, Robbins, & Müller, 2007; Lane et al., 2008), but to date it remains unknown which specific genetic influences might be involved in mindfulness.

There are also a number of non-shared environmental influences that might be relevant in the aetiology of cognitive impairment and cognitive biases. First, negative experiences and life events might lead to the development of negative and maladaptive associations that could

underpin cognitive biases. For example, previous studies found that children who experienced maltreatment are more likely to have attentional bias to threat (Pine et al., 2005; Pollak et al., 2000). Stressful life events, including events related to health, have been implicated in the aetiology of anxiety sensitivity (McLaughlin & Hatzenbuehler, 2009; Zavos, Wong, et al., 2012). Second, some studies have found that negative information about stimuli used in experimental tasks can significantly increase cognitive biases (Field, 2006; Haddad, Lissek, Pine, & Lau, 2011). This suggests that young people can acquire maladaptive cognitions through interactions with peers or parents that entail exchange of threatening information and criticism. In support of this view, other studies have found that parental overcontrol and parental modelling of threatening interpretations could increase biased cognitive processes in children (Bogels & Brechman-Toussaint, 2006; Dadds, Barrett, Rapee, & Ryan, 1996; Lester, Seal, Nightingale, & Field, 2010). Parenting style might also be important in the development of executive functions (Bernier, Carlson, Deschênes, & Matte-Gagné, 2012; Bibok, Carpendale, & Müller, 2009; Hughes, 2011). Specifically to the aetiology of mindfulness, some of the environmental influences might also include cultural exposure and meditation-related training.

The results in chapters 5 and 6 also provide novel information about aetiological influences common to cognitive processes and internalizing symptoms. First, the results in chapter 5 extend the existing evidence that total anxiety sensitivity, depression and anxiety share genetic overlap (Eley et al., 2007; Waszczuk et al., 2013; Zavos et al., 2010) by showing that this pattern of results holds for each anxiety sensitivity subscale individually with relation to both depression and anxiety (with some specificity observed for physical concerns, discussed above). Furthermore, a similar pattern of both high genetic overlap, and moderate non-shared environmental correlations between anxiety sensitivity subscales, depression and anxiety was observed in childhood, adolescence and young adulthood. This indicates developmental stability of the aetiological influences shared between anxiety sensitivity and internalizing symptoms. Interestingly, these results are somewhat in contrast to the relatively

developmentally dynamic pattern of aetiological associations shared between depression and different anxiety types observed in chapters 3 and 4. This might be because anxiety sensitivity is not characterised by notable genetic innovation and attenuation across adolescence and young adulthood, and even non-shared environmental influences on anxiety sensitivity have been found to be considerably stable (Zavos, Gregory, et al., 2012). Thus, the stable aetiology of anxiety sensitivity might to some degree explain comparable aetiological associations between anxiety sensitivity subscales, depression and anxiety at multiple developmental stages. Furthermore, stable cognitive biases might also contribute to the homotypic and heterotypic continuity of internalizing problems.

Second, multivariate twin modelling analyses in chapter 6 revealed that mindfulness and depressive symptoms share moderate genetic and small non-shared environmental correlations in adolescence. Latent genetic influences account for over half of the moderate phenotypic association between mindfulness and depression. Mindfulness was also found to be characterized by significant unique influences, with about two thirds of genetic factors and almost all non-shared environmental factors being independent of depressive symptoms. This is in line with a growing body of research suggesting that mindfulness is associated with a range of other constructs over and above its link with depressive symptoms and anxiety sensitivity (Brown & Ryan, 2003; Giluk, 2009).

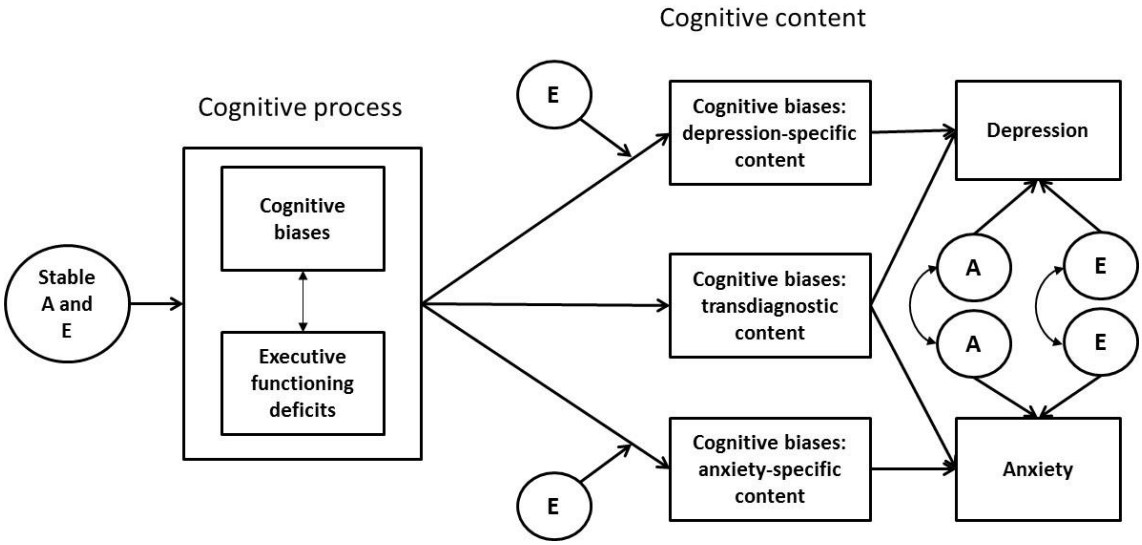
Overall, the results suggest that associations between cognitive processes such as anxiety sensitivity and mindfulness, and internalizing problems can be explained largely by underlying genetic liability, in line with the generalist genes hypothesis (Eley, 1997). The results are suggestive of common genetic vulnerability to impaired and biased cognitions and to internalizing symptoms, and imply that there might be a biological pathway linking these phenotypes. Recent studies point to epigenetic regulation of inflammatory pathways as one of the pathways underpinning mindfulness-based interventions (Kaliman et al., 2014). Other biological pathways associated with mindfulness that may be important in internalizing

disorders could include regulation of brain, endocrine and immune function (Creswell et al., 2007; Ludwig & Kabat-Zinn, 2008). Finally, these results are in line with evidence that other cognitive biases, such as attributional style and rumination, also share genetic vulnerability with internalizing problems (Chen & Li, 2013; Eley, Gregory, et al., 2008; Lau et al., 2014; Lau & Eley, 2008a; Moore et al., 2013; Zavos et al., 2010).

8.3.3. THEORETICAL MODEL

The aim of a model presented in Figure 8.1 is to integrate both empirical results from the current thesis and relevant literature in the field into a single theoretical framework, in the light of the research question central to the thesis: how do genes, environments and cognitions contribute to the co-occurrence of depression and anxiety across development? The model extends previous cognitive and genetic models proposed to explain vulnerability to depression (Beck, 2008; Gibb, Beevers, & McGeary, 2013; Hankin & Abramson, 2001) by considering these processes from a transdiagnostic perspective and by combining them with generalist genes and cognitive content specificity hypotheses.

Figure 8.1 – Theoretical model of genetic, environmental and cognitive factors in the development of depression and anxiety.



First, it is proposed that there are broad and developmentally stable genetic, and to a lesser extent, environmental influences on cognitive processes and internalizing symptoms. These aetiological influences are thought to underpin individual differences in executive functioning and cognitive biases, with individuals with poorer cognitive control more vulnerable to develop cognitive processing biases in the context of emotional information, and vice versa. The relationship between cognitive control deficits and cognitive biases is likely to be bidirectional, but together these maladaptive cognitive processes characterise both depression and anxiety symptoms. The cognitive processes are proposed to be stable across development and thus contribute to the continuity of internalizing symptoms over time.

Second, evidence discussed in this thesis suggests that there are both transdiagnostic and disorder-specific contents of cognitive biases. Cognitive biases with transdiagnostic cognitive contents, such as mental concerns in anxiety sensitivity, contribute to the co-occurrence of depression and anxiety. Biases with disorder-specific contents contribute to the differentiation between depression and anxiety. The content specificity is proposed to arise due to disorder-

specific environmental influences, for example a threatening life event might lead to physical concerns in anxiety sensitivity in a vulnerable individual, contributing uniquely to anxiety symptoms.

Third, there are disorder-specific genetic and environmental influences on depression and anxiety that contribute to differentiation between these disorders. Disorder-specific genetic influences are generally time-specific and small in magnitude, except for childhood where the genetic influences on depression and anxiety are more distinct. Disorder-specific environmental influences are substantial and largely time-specific. These disorder-specific genetic and environmental influences are proposed to contribute to the change in symptoms over time. In adults, the distinction between distress and fear disorders might be more suitable than depression versus anxiety. Finally, since there can be other possible sources of shared genetic and environmental influences between anxiety and depression that do not act via executive functioning and cognitive biases, disorder-specific influences are allowed to correlate.

Taken together, depression and anxiety co-occur across development due to shared stable genetic and to a lesser extent environmental influences. Influence of these shared aetiological risk factors on depression and anxiety acts via executive functioning deficits and biased cognitive processes that broadly contribute to development, maintenance and co-occurrence of internalizing symptoms. While some biased cognitive processing is characterised by transdiagnostic content that contributes to depression and anxiety comorbidity, disorder-specific environmental influences contribute to disorder-specific cognitive biases contents that uniquely influence depression and anxiety symptoms. There are also disorder-specific genetic and environmental influences on depression and anxiety that contribute to change in symptoms over time.

It is important to note some of the key limitations of the proposed model. First, it is based largely on evidence from cross-sectional research, especially in the field of cognitive processing. While causal paths are assumed from cognitions and environmental influences to internalizing symptoms, reverse and bidirectional relationship between them might be possible (although note mixed empirical support for the scar hypothesis in depression and anxiety (Rohde, Lewinsohn, & Seeley, 1990; Zavos, Rijsdijk, et al., 2012; Zeiss & Lewinsohn, 1988)). Second, the hypothesis that specific environmental experiences influence the differential development of anxiety and depression by altering the content of cognitive processing biases is largely tentative at present. Third, future research on age differences in the aetiology of cognitive processes in internalizing problems needs to investigate why maladaptive thought processes overlap in childhood despite largely separate genetic influences on depression and anxiety at that age.

8.3.4. Clinical implications

The research described in this thesis carries a number of clinical implications. First, it provides empirical evidence relevant to the debate about the transdiagnostic treatment of depression and anxiety, designed to target common elements of these disorders in one protocol. The evidence for shared genetic and environmental aetiology between depression and anxiety is in agreement with the findings that internalizing disorders respond to similar interventions and therapies (Barlow et al., 2014; Farchione et al., 2012; McEvoy et al., 2009; Titov et al., 2011). The findings in chapter 4 that depression and different anxiety types are characterised by considerable heterotypic continuity, which is underpinned by stable genetic and to a lesser extent environmental influences, additionally suggests that transdiagnostic approaches might have a longitudinal benefit and may be suitable for preventing comorbid disorders in the

future. This is in line with the results from chapters 5-7 which show that many cognitive processes that are targeted by approaches such as CBT characterise both depression and anxiety at all developmental stages. However, some of notable age differences observed in chapter 3 analyses suggest that while transdiagnostic treatment focused on a range of symptoms common to internalizing disorders may be more appropriate for adolescent and adult patients, disorder-specific approaches may be more appropriate for children.

Second, investigations into the cognitive content specificity hypothesis provide valuable insights for tailoring the content of transdiagnostic versus disorder-specific treatments. The results in chapter 5 suggest that *physical concerns* dimension of anxiety sensitivity, which relates to the *fear* of biological and bodily symptoms of distress, are central to anxiety but not so typical of depression. This makes them relevant to anxiety-focused treatments but probably less appropriate for transdiagnostic or depression-specific approaches. Conversely, *mental* and *social concerns* showed independent associations with both anxiety and depression, especially in adolescence and adulthood, suggesting that concerns surrounding cognitive and social symptoms are important in both anxiety and depression. Targeting these maladaptive concerns seems appropriate for transdiagnostic treatments of internalizing disorders. Age differences were notable, with stronger associations between social concerns and internalizing problems in adolescence than in childhood and adulthood. This suggests that targeting social concerns may be most useful in adolescent depression. Further investigation into the shared and disorder-specific cognitions would be beneficial for therapeutic purposes. Future clinical research and practice should also explore shared and specific cognitive content of different anxiety types to inform targeted treatment of different symptoms of anxiety.

The third clinical implication of the current research concerns the role of executive function in therapy. Chapters 6 and 7 explored the relationship between cognitive control and cognitive biases and found that both are similarly linked to internalizing symptoms in young people. Although the current research was cross-sectional, the results are in line with evidence that

attentional training might be a potential treatment and prevention approach for internalizing problems (Callinan et al., 2014; Roughan & Hadwin, 2011). Furthermore, mindfulness training might be especially useful in depression prevention and treatment in young people by means of improving attentional control (Burke, 2010). This might be because cognitive training reduces cognitive biases (Hoorelbeke et al., 2015), however the directionality of this relationship and the effectiveness of the training is still debated (Cristea et al., 2015; Shipstead et al., 2012; Wass et al., 2012). Future research should explore whether established therapies such as CBT, as well as novel approaches such as attentional bias modification, improve overall attentional control. This could provide novel insight into mechanisms of action underpinning these therapeutic processes (Cisler & Koster, 2010). Finally, executive control training might be a particularly suitable approach in children and adolescents given that younger participants seem to benefit more from cognitive training than adults (Wass et al., 2012), possibly reflecting greater neural and behavioural plasticity earlier in development (Blakemore, 2008). Cognitive training in young people might also carry an additional benefit of transfer effect to other aspects of functioning such as academic achievement (Best, Miller, & Naglieri, 2011; Goldin et al., 2014).

Fourth, substantial non-shared environmental influences on internalizing traits and related cognitions suggest that future studies should focus on identifying these specific environmental factors. Known environmental risk factors can be targeted directly by therapeutic and resilience approaches. This is especially relevant for environmental factors that contribute to the developmental stability and overlap between symptoms, as modifying these environmental influences might be most beneficial and long lasting. However, given that environmental influences were found to be largely time specific, any interventions that target environmental stressors might only be effective over a short period of time. This suggests that repeated interventions over the course of development might be more effective than a single dose of treatment. Conversely, clinical and resilience interventions that tap into stable

cognitive processes might have more long lasting impact. Finally, identifying specific genetic influences implicated in the aetiology of internalizing problems and maladaptive cognitions would have important implications for personalized medicine, for example by allowing prediction of treatment response (Eley et al., 2012; Keers & Aitchison, 2011; Lester & Eley, 2013).

Finally, the results have implications for psychiatric taxonomy and diagnostic systems such as DSM-5. They support the view that overlapping as well as unique aspects of depression and different anxiety types should be acknowledged in diagnostic manuals. Age-related differences in the aetiology of depression and anxiety symptom clusters, as well as in the associations between these traits, suggests that a more developmentally sensitive nosology system might be needed. Thus, the current results affirm the need to continue examining developmental differences in the quantitative genetics of depression and different anxiety disorders, to ensure that the diagnostic conceptualization of psychopathology is age-appropriate.

8.3.5. FUTURE DIRECTIONS

Current results can be extended in several ways to further inform main themes of this thesis. First, future avenues for twin modelling and molecular genetics studies are outlined. Next, ideas about further work on the cognitive content specificity hypothesis are proposed. Finally, novel directions for research on the relationship between cognitive control and biases are discussed.

Twin modelling studies

The results presented in this thesis highlight several avenues for future twin modelling research. First, results in chapters 3 and 4 demonstrate the value of focusing on the

heterogeneity of anxiety disorders in longitudinal quantitative genetic research, in order to gain an in-depth understanding of similarities between different anxiety types, as well as the disorder-specific aetiology and developmental course of each type of anxiety. Future twin modelling research should include a wider variety of internalizing symptoms to comprehensively study the higher order genetic structure, as well as stability, of these problems across development and in adulthood. Some of the symptoms that would be very interesting to study from this perspective are specific phobias and pre- versus post-adolescence onset depression symptoms. These genetically informed analyses should also be extended to incorporate other types of psychopathology, such as PTSD, OCD, psychotic and externalizing symptoms. For example, the evidence suggests that bipolar disorder forms a separate higher order factor alongside distress and fear (Watson, 2005), and it would be interesting to investigate whether bipolar disorder is influenced by a separate set of genes. Additionally, research looking at internalizing and externalizing symptoms together generally finds that they are underpinned by a single liability factor and share substantial common genetic influences (Cosgrove et al., 2011; Lahey et al., 2011; O'Connor, McGuire, Reiss, Hetherington, & Plomin, 1998; Rowe, Rijsdijk, Maughan, Hosang, & Eley, 2008; Subbarao et al., 2008), while a recent longitudinal twin study found that genetic influences on externalizing problems at 5 years continue to influence internalizing problems at 12 years (Wertz et al., 2014). However, the genetic architecture underpinning these comorbidities across development remains largely unknown. Finally, the role of personality traits in the higher order structures should also be explored from twin modelling perspective, given a high genetic overlap between certain personality traits such as neuroticism, and a range of internalizing symptoms (Bienvenu, Hettema, Neale, Prescott, & Kendler, 2007; Hansell et al., 2012; Hettema et al., 2006).

Second, twin modelling approaches should continue to be used to gain in-depth insight into the aetiology of mindfulness. The current thesis focused on the attentional control aspect of

mindfulness, but future twin studies should use other measures that capture more diverse aspects of mindfulness, such as the non-judgemental attitude. A higher order genetic structure of mindfulness should be investigated to inform whether a range of cognitive processes thought to underpin mindfulness have common or unique aetiology. Additionally, it would be interesting to study whether the heritability of mindfulness changes across the lifespan. Furthermore, as longitudinal and developmental studies of mindfulness are very rare, it would be interesting for future research to focus on the phenotypic and aetiological stability of this trait. Similarly, longitudinal studies could also be conducted for anxiety sensitivity across the lifespan in order to add to the growing evidence about the contribution of stable and time-specific genetic and environmental influences over time. The aetiological associations between different cognitive phenotypes, such as executive functioning and biases, could also be explored. Finally, further multivariate twin studies could be conducted in order to investigate the aetiological relationship between the cognitive phenotypes such as mindfulness and anxiety sensitivity, and internalizing symptoms, both within-time and longitudinally.

Molecular genetic studies

Molecular genetic studies might be able to identify specific genetic variants influencing depression and anxiety. To date a number of candidate genes have been implicated in internalizing problems, for example 5-HTTLPR, Val158Met polymorphism of catechol-O-methytransferase (COMT) and brain-derived neurotrophic factor (BDNF), but genome-wide association (GWA) studies have to date not found significant associations (Cohen-Woods, Craig, & McGuffin, 2013; Flint & Kendler, 2014; Ripke et al., 2013). High genetic correlations between depression and anxiety symptoms indicate that molecular research might be able to identify pleiotropic genetic variants implicated in these problems. Thus, studying internalizing symptoms together might increase power to detect shared susceptibility loci for these disorders (Hettema, Chen, Sun, & Brown, 2015). However, the difference in genetic results pre- and post-adolescence, and the developmentally dynamic nature of genetic influences, in

particular the genetic attenuation and innovation seen in adolescence, suggests that some genetic influences may be important only at one developmental stage. This suggests that stratifying samples by age may reduce heterogeneity and could help to identify time-specific genetic variants (Traylor, Markus, & Lewis, 2014; Zaitlen et al., 2012).

Future candidate gene studies might benefit from exploring the role of the 5-HTTLPR in maladaptive cognition further, as well as focusing on other candidate genetic variants that have been implicated in depression and anxiety. Another approach would be to conduct GWA studies of cognitive phenotypes relevant to internalizing symptoms, although such research might not currently be realistic given large sample sizes required. However, if the role of specific genes in the aetiology of internalizing symptoms and maladaptive cognition becomes clearer, it might be possible to combine the genetic markers together to create polygenic risk scores to predict an individual's vulnerability to depression and anxiety (Demirkan et al., 2011). Finally, future molecular work is needed to further current understanding of the mechanisms underpinning genetic innovation and attenuation throughout development. Complex interactions between genetic and environmental influences on cognition should also be explored.

The twin modelling results could also be replicated using other methods informed by molecular genetics, such as Genome-wide Complex Trait Analysis (GCTA) (Yang, Lee, Goddard, & Visscher, 2011; Yang, Manolio, et al., 2011). Using GCTA, adult major depressive disorder (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Lubke et al., 2012) and childhood anxiety (Trzaskowski et al., 2013) and internalizing problems (Benke et al., 2014) have been found to be moderately heritable, consistently with the estimates obtained by twin studies. However, to date no study has investigated the genetic correlations between different anxiety types as well as depression using GCTA method at any age. The genetic contribution to the stability of the symptoms has not been investigated using this method either.

Cognitive content-specificity hypothesis

The specificity of cognitive processes and cognitive contents involved in depression and anxiety should also be studied in more detail. First, it remains unclear to what extent cognitive *processes* are as broad as proposed by *cognitive content-specificity hypothesis*. While cognitive biases such as attentional bias towards threat or anxiety sensitivity studied in this thesis seem to constitute a transdiagnostic process, other maladaptive thought processes such as hopelessness might be unique to specific domains of internalizing symptoms (Beck et al., 2006; Beck et al., 2001; Miranda & Mennin, 2007). Furthermore, very few studies have focused on unique associations between different executive functions and internalizing symptoms. The limited studies that researched this issue sometimes find a degree of specificity (Beaudreau & O'Hara, 2009; Lyche et al., 2011; Thomas et al., 2009), indicating that this question needs further investigation. Future studies should also investigate whether the processes related to mindfulness are transdiagnostic or specific to depression or anxiety.

Second, much more work is needed to establish to what degree depression and anxiety differ in the *content* of cognitive biases. Although the evidence suggests that some content of cognitive biases might be specific to depression or anxiety, boundaries are unclear and it appears that there is also a great deal of overlap in cognitive content. Furthermore, none of the studies investigated the role of cognitive content in executive functioning, and whether cognitive control of different types of non-emotional information (for example future versus past oriented stimuli) might be uniquely associated with depression and anxiety.

Finally, the vast majority of studies that investigated the specificity of processes and contents of cognitive control and biases to depression and anxiety, including the work presented in this thesis, did not look at differential associations with different anxiety types. Future research into cognitive content specificity should address the issue of heterogeneity of anxiety disorders in order to provide more insight into the common as well as the unique features of each

anxiety type. Some of the initial work in this area suggests that significant differences between different anxiety types may be observed (Harvey et al., 2004; Mogg et al., 2015). Expanding this work to investigate common and shared cognitive processes and contents in distress versus fear disorders is another avenue for future research.

Relationship between cognitive control and biases

The relationship between anxiety sensitivity and mindfulness explored in chapter 6 should be studied in more depth. For example, the direction of relationship between these constructs has only been tested in two studies in adults, which have found that mindfulness training might reduce anxiety sensitivity symptoms, possibly by reducing experiential avoidance (McCracken & Keogh, 2009; Vujanovic et al., 2007). It is unclear whether anxiety sensitivity has an impact on mindfulness disposition, and whether proposed mechanisms are applicable to young people. Future longitudinal studies should also investigate whether other kinds of cognitive training can reduce anxiety sensitivity symptoms, as it is unclear which aspects of mindfulness, such as the awareness of the present moment experience or the non-judgemental attitude, might be important in the reduction of anxiety sensitivity. The relationship between mindfulness and different anxiety sensitivity subscales also remains unknown. In addition, this research should also focus on understanding mechanisms through which mindfulness and anxiety sensitivity interact to influence internalizing symptoms. The direction of the associations and possible causal links between mindfulness, depression and anxiety sensitivity need to be explored in future longitudinal studies.

The relationship between attentional control and attentional biases investigated in chapter 7 should also be explored further. The finding that childhood anxiety and depression are characterized by both attentional control deficits and attentional biases suggests that future studies should investigate the cognitive mechanisms linking these two processes. For example longitudinal research should establish whether attentional biases and attentional control are

different facets of the same deficit, or whether they are separate impairments that overlap or interact. The unique as well as combined influence of attentional control and attentional biases on depression and anxiety should be explored. Finally, it is unclear whether the results obtained in chapter 7 generalize to other ages. Attentional control theory should be investigated longitudinally to clarify age-related changes in cognitive control and its associations with attentional biases and internalizing symptoms across development. Looking particularly at younger children might provide insights into the developmental trajectory and potential directionality of these processes. Taken together, one of the exciting avenues for future research, building on the work presented in this thesis, would be to comprehensively explore the relationship between different types of executive functioning and cognitive biases in the context of pathogenesis of depression and anxiety.

8.4. General limitations

Self-report measures

There is a range of limitations associated with self-report measures used in all of the empirical chapters. First, there are concerns associated with the use of self-report questionnaires in children. The extent to which children can understand and report on their internalising symptoms is debated. Nevertheless, it has been demonstrated that children as young as 8 years old can make valid reports of internalizing symptoms (Merrell, McClun, Kempf, & Lund, 2002; Michael & Merrell, 1998) and interpretations of anxiety symptoms (Muris, Hoeve, Meesters, & Mayer, 2004). As internalising problems are sometimes difficult to observe, this method may be more reliable than data from parental reports. All questionnaires used in this thesis were validated in similar samples and had adequate internal consistencies (see section

2.3). Furthermore, the results obtained in children are similar at ages 8 and 10 years old, once again supporting the validity of the measures used.

It is also debated whether children are able to cognitively experience and understand the concept of anxiety sensitivity (Chorpita, Albano, & Barlow, 1996). Some have argued that children under 11 years are too young to have developed the cognitive capacity to understand the abstract link between present internal sensations and consequences in the future. Contrary to this view, questionnaires such as CASI have been validated in child populations (Silverman et al., 1991). Many studies have found significant continuity of anxiety sensitivity symptoms across childhood, as well as showed that anxiety sensitivity can predict future anxiety symptoms when accounting for current anxious state (Rabian, Embry, & MacIntyre, 1999; Weems, Hammond-Laurence, Silverman, & Ginsburg, 1998). Taken together, the evidence confirms that questionnaire measures capture internalizing symptoms and anxiety sensitivity in child populations. However, including measures from multiple observers at these waves could have strengthened the findings.

Second, another limitation related to using self-report measure of anxiety sensitivity is that the *social* and *mental concerns* dimensions only contain three or two items, resulting in lower internal consistency. They also may not have comprehensively captured the breath of concerns surrounding social and cognitive aspects of experiencing anxiety symptoms. However, the CASI is currently the only available self-report measure of anxiety sensitivity in young people. Given the considerable evidence for a multifaceted construct, expanding childhood measures of anxiety sensitivity to better capture *social* and *mental* concerns would be beneficial.

Third, there are also limitations specific to the self-report mindfulness measure. It remains debated whether mindfulness can be accurately assessed using self-report questionnaires, and it has been suggested that it may be better captured by measures such as interviews

(Grossman, 2011). Although there are no objective markers of mindfulness that questionnaires could be validated against, self-report mindfulness has been negatively associated with behavioural measures of related constructs, such as mind wandering (Mrazek, Smallwood, & Schooler, 2012) and attention lapses (Cheyne, Carriere, & Smilek, 2006). Furthermore, the current thesis used a relatively narrow definition of mindfulness in terms of attentional processing, but it did not capture other facets of the trait, such as the non-judgmental and accepting attitude (Grossman, 2011), limiting the interpretability of the results. However, the focus on attentional control allowed more precise investigations of one specific cognitive mechanism central to mindfulness and its association with depression and anxiety sensitivity.

Fourth, different anxiety measures were used at different waves to ensure that inventories were age appropriate. Although measurement invariance was not formally tested, longitudinal associations suggest a comparable continuity of scores within and across different measures, in line with the view that they measure the same underlying constructs. Finally, an additional limitation of self-report data is that it could have inflated non-shared environmental correlations due to shared measurement error. The shared method variance might have also confounded the results as individuals who report one type of internalizing problems are more likely to report other types of internalizing and cognitive problems, inflating correlations between variables. Once again future research might benefit from the use of multiple informers.

Sample attrition

A limitation of large longitudinal samples is that there are problems with sample attrition, as discussed in section 2.2. For example lower response rates and retention were observed in families from socially disadvantages backgrounds. G1219 participants had on average higher socio-economic status than the general population, and housing tenure and education both predicted attrition. Some of these methodological biases were corrected by adding a weight to

the genetic analyses (in ECHO sample), but to allow comparisons with other samples, the weighting variable was not applied to the phenotypic analyses. The weight did not have any significant impact on the analyses. Furthermore, it does not account for the fact that samples might not be entirely representative of social extremes. In order to account for problems associated with the missing data, OpenMx uses raw data modelling with maximum likelihood approach, which uses all available data to estimate variance but only data from complete pairs to calculate covariance.

Sample size

There are some limitations related to small sample sizes in childhood. First, although considered large for phenotypic analyses, the ECHO sample had reduced power to examine sex differences or shared environmental influences, and parameter estimates had large confidence intervals. However, results of a recent study suggest that genetic influences on symptoms of anxiety in males and females are very similar in childhood (Kendler, Gardner, & Lichtenstein, 2008), and no evidence for qualitative or quantitative sex differences were found in adolescent samples (except for depression in TEDS). Additionally, based on the MZ and DZ correlations, shared environmental influences were not expected to emerge, and some of the recent studies found no evidence for shared environmental influences on anxiety in middle childhood (Kendler, Gardner, & Lichtenstein, 2008; Ogliari et al., 2010). Shared environmental effects are much more likely to emerge in the studies that use parental report rather than self-report data. Nevertheless, replication in larger pediatric twin samples is essential. However, given internal replication of results across the two time points, the sample size should not be a considerable limitation for interpretation of twin modelling results in the child sample.

The sample in the attentional control study (chapter 7) was also small and underpowered to investigate sex differences or detect small effects. This might be the reason why statistically significant differences in the magnitudes of the correlations between internalizing symptoms

and distractor costs due to non-emotional and emotional distractors were not detected. However, effect sizes were similar for each of these comparisons. Overall, the experimental results should be replicated in a larger sample.

Age ranges

The inclusion of siblings in G1219 study meant that there were large age ranges in adolescence and early adulthood. This limits the conclusions about patterns of associations across development in the cross-sectional results. However, 72% of the participants were twins with much narrower, non-overlapping age ranges. Additional analyses excluding siblings in chapter 3 suggest that the results are applicable to tighter age-ranges. The advantage of inclusion of siblings is that it enhances the generalizability of the findings to non-twin populations.

Non-clinical samples

Findings from analyses addressing psychopathological questions in non-clinical samples do not necessarily apply to clinical populations. Moreover, current analyses involved average differences between individuals in a given population and they are not necessarily valid to single clinical cases or individuals. To inform understanding of internalizing disorders and related cognitions in clinical settings, the results should be replicated in clinical samples with comorbid diagnoses and using lifetime diagnostic interviews. However, internalizing symptoms are important markers of psychopathology (Balázs et al., 2013; Fergusson et al., 2005; Pickles et al., 2001) and given that common mental disorders are quantitative traits (Plomin, Haworth, & Davis, 2009), there is evidence that differently defined internalizing problems have the same etiology (Kendler, Heath, Martin, & Eaves, 1987; Kendler et al., 1992b; Kendler, Neale, Kessler, Heath, & Eaves, 1992c).

Cross-sectional analyses

Although analyses in chapter 3 were followed up with longitudinal analyses in chapter 4, the remaining three empirical chapters were only cross-sectional. Cross-sectional analyses allow the examination of concurrent relationships between variables. However, they are unable to establish causality. Furthermore, age-related, developmental changes in phenotypic and genetic associations between cognitive constructs and internalizing symptoms used in the analyses remain to be explored in future prospective studies.

Twin modelling limitations

Finally, there are limitations inherent to the twin design, discussed comprehensively in section 2.2.5. These have minimal and contrasting effects on parameter estimates which should therefore be taken as indicative rather than absolute. To further support the results presented in this thesis, it would be interesting to investigate research questions using novel genetically sensitive approaches such as GCTA that do not rely on twin modelling assumptions and limitations.

8.5. CONCLUSIONS

The current thesis used genetically informative, longitudinal and experimental approaches to investigate two important aspects of the association between depression and anxiety. First, it focused on the shared aetiology of depression and four anxiety types across development. The results provided evidence for developmental differences in the aetiology of this relationship, and elucidated the pattern of stable and time-specific genetic and environmental influences on these symptoms over time. The second approach concerned the role of cognitive vulnerabilities in the development of both depression and anxiety. Disorder-specific versus

shared cognitive processes and content in depression and anxiety were identified at different developmental stages. Furthermore, aetiological influences shared between cognitive vulnerabilities and internalizing symptoms were explored. The results carry a number of implications for future research and clinical practice.

REFERENCES

AACAP. (2007a). Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 46*(2).

AACAP. (2007b). Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 46*(11).

Achenbach, T. M., & Edelbrock, C. S. (1978). The classification of child psychopathology: a review and analysis of empirical efforts. *Psychological Bulletin, 85*(6), 1275.

Adegbite, A. L., Castille, S., Ward, S., & Bajoria, R. (2004). Neuromorbidity in preterm twins in relation to chorionicity and discordant birth weight. *American Journal of Obstetrics and Gynecology, 190*(1), 156-163.

Ahrens, A. H., & Haaga, D. A. (1993). The specificity of attributional style and expectations to positive and negative affectivity, depression, and anxiety. *Cognitive Therapy and Research, 17*(1), 83-98.

Airaksinen, E., Larsson, M., & Forsell, Y. (2005). Neuropsychological functions in anxiety disorders in population-based samples: evidence of episodic memory dysfunction. *Journal of Psychiatric Research, 39*(2), 207-214.

Allen, L. B., White, K. S., Barlow, D. H., Shear, M. K., Gorman, J. M., & Woods, S. W. (2010). Cognitive-behavior therapy (CBT) for panic disorder: Relationship of anxiety and depression comorbidity with treatment outcome. *Journal of Psychopathology and Behavioral Assessment, 32*(2), 185-192.

Alloy, L. B., Abramson, L. Y., Whitehouse, W. G., Hogan, M. E., Tashman, N. A., Steinberg, D. L., . . . Donovan, P. (1999). Depressogenic cognitive styles: predictive validity, information

processing and personality characteristics, and developmental origins. *Behaviour Research and Therapy, 37*(6), 503-531.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders, DSM-5* (Fifth ed.). Arlington, VA: American Psychiatric Publishing.

Anda, R. F., Felitti, V. J., Bremner, J. D., Walker, J. D., Whitfield, C., Perry, B. D., . . . Giles, W. H. (2006). The enduring effects of abuse and related adverse experiences in childhood. *European Archives of Psychiatry and Clinical Neuroscience, 256*(3), 174-186.

Anderson, E. R., & Hope, D. A. (2008). A review of the tripartite model for understanding the link between anxiety and depression in youth. *Clinical psychology review, 28*(2), 275-287.

Anderson, E. R., Veed, G. J., Inderbitzen-Nolan, H. M., & Hansen, D. J. (2010). An evaluation of the applicability of the tripartite constructs to social anxiety in adolescents. *Journal of Clinical Child & Adolescent Psychology, 39*(2), 195-207.

Angold, A., Costello, E. J., & Erkanli, A. (1999). Comorbidity. *Journal of child psychology and psychiatry, 40*(1), 57-87.

Angold, A., Costello, E. J., Messer, S. C., Pickles, A., Winder, F., & Silver, D. (1995). The development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. *International Journal of Methods in Psychiatric Research, 5*, 1-12.

Ansari, T. L., Derakshan, N., & Richards, A. (2008). Effects of anxiety on task switching: Evidence from the mixed antisaccade task. *Cognitive, Affective, & Behavioral Neuroscience, 8*(3), 229-238.

Asarnow, J. R., Emslie, G., Clarke, G., Wagner, K. D., Spirito, A., Vitiello, B., . . . Asarnow, J. R. j. m. u. e. (2009). Treatment of selective serotonin reuptake inhibitor-resistant depression in adolescents: Predictors and moderators of treatment response.

[References]. *Journal of the American Academy of Child and Adolescent Psychiatry, .48*(3).

Asselmann, E., Wittchen, H.-U., Lieb, R., Höfler, M., & Beesdo-Baum, K. (2015). Danger and loss events and the incidence of anxiety and depressive disorders: a prospective-longitudinal community study of adolescents and young adults. *Psychological Medicine, 45*, 153–163.

Avenevoli, S., Stolar, M., Li, C., Dierker, L. C., & Merikangas, K. R. (2001). Comorbidity of Depression in Children and Adolescents: Models and Evidence from a ProspectiveHigh-Risk Family Study. *Society of Biological Psychiatry, 49*, 1071-1081.

Axelson, D. A., & Birmaher, B. (2001). Relation between anxiety and depressive disorders in childhood and adolescence. *Depression and anxiety, 14*(2), 67-78.

Baddeley, A. (1996). Exploring the central executive. *The Quarterly Journal of Experimental Psychology: Section A, 49*(1), 5-28.

Balázs, J., Miklósi, M., Keresztény, Á., Hoven, C. W., Carli, V., Wasserman, C., . . . Cosman, D. (2013). Adolescent subthreshold-depression and anxiety: psychopathology, functional impairment and increased suicide risk. *Journal of child psychology and psychiatry, 54*(6), 670-677.

Banich, M. T., Mackiewicz, K. L., Depue, B. E., Whitmer, A. J., Miller, G. A., & Heller, W. (2009). Cognitive control mechanisms, emotion and memory: a neural perspective with implications for psychopathology. *Neuroscience & Biobehavioral Reviews, 33*(5), 613-630.

Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M. J., & van Ijzendoorn, M. H. (2007). Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. *Psychological Bulletin, 133*(1), 1-24.

Barlow, D. H., Sauer-Zavala, S., Carl, J. R., Bullis, J. R., & Ellard, K. K. (2014). The nature, diagnosis, and treatment of neuroticism back to the future. *Clinical Psychological Science, 2*(3), 344-365.

Barnes, J., & Boutwell, B. B. (2013). A demonstration of the generalizability of twin-based research on antisocial behavior. *Behavior Genetics, 43*(2), 120-131.

Barnett, J., Jones, P., Robbins, T., & Müller, U. (2007). Effects of the catechol-O-methyltransferase Val158Met polymorphism on executive function: a meta-analysis of the Wisconsin Card Sort Test in schizophrenia and healthy controls. *Molecular Psychiatry, 12*(5), 502-509.

Barrett, P. M., Rapee, R. M., Dadds, M. M., & Ryan, S. M. (1996). Family enhancement of cognitive style in anxious and aggressive children. *Journal of Abnormal Child Psychology, 24*, 187-203.

Basso, M. R., Lowery, N., Ghormley, C., Combs, D., Purdie, R., Neel, J., . . . Bornstein, R. (2007). Comorbid anxiety corresponds with neuropsychological dysfunction in unipolar depression. *Cognitive Neuropsychiatry, 12*(5), 437-456.

Batink, T., Peeters, F., Geschwind, N., van Os, J., & Wichers, M. (2013). How does MBCT for depression work? Studying cognitive and affective mediation pathways. *PloS one, 8*(8), e72778.

Baune, B. T., McAfoose, J., Leach, G., Quirk, F., & Mitchell, D. (2009). Impact of psychiatric and medical comorbidity on cognitive function in depression. *Psychiatry and Clinical Neurosciences, 63*(3), 392-400.

Beard, C., Sawyer, A. T., & Hofmann, S. G. (2012). Efficacy of attention bias modification using threat and appetitive stimuli: A meta-analytic review. *Behavior Therapy, 43*(4), 724-740.

Beaudreau, S. A., & O'Hara, R. (2008). Late-life anxiety and cognitive impairment: a review. *The American Journal of Geriatric Psychiatry, 16*(10), 790-803.

Beaudreau, S. A., & O'Hara, R. (2009). The association of anxiety and depressive symptoms with cognitive performance in community-dwelling older adults. *Psychology and Aging, 24*(2), 507.

Beblo, T., Sinnamon, G., & Baune, B. T. (2011). Specifying the neuropsychology of affective disorders: clinical, demographic and neurobiological factors. *Neuropsychology Review, 21*(4), 337-359.

Beck, A. T. (2008). The evolution of the cognitive model of depression and its neurobiological correlates. *American Journal of Psychiatry, 165*(8), 969-977.

Beck, A. T., Brown, G., Steer, R. A., Eidelson, J. I., & Riskind, J. H. (1987). Differentiating anxiety and depression: A test of the cognitive content-specificity hypothesis *Journal of Abnormal Psychology, 96*, 179-183.

Beck, A. T., Steer, R. A., Beck, J. S., & Newman, C. F. (1993). Hopelessness, depression, suicidal ideation, and clinical diagnosis of depression. *Suicide and Life-Threatening Behavior, 23*(2), 139-145.

Beck, A. T., Wenzel, A., Riskind, J. H., Brown, G., & Steer, R. A. (2006). Specificity of hopelessness about resolving life problems: Another test of the cognitive model of depression. *Cognitive Therapy and Research, 30*(6), 773-781.

Beck, R., Benedict, B., & Winkler, A. (2003). Depression and anxiety: Integrating the tripartite and cognitive content-specificity assessment models. *Journal of Psychopathology and Behavioral Assessment, 25*(4), 251-256.

Beck, R., & Perkins, T. S. (2001). Cognitive content-specificity for anxiety and depression: A meta-analysis. *Cognitive Therapy and Research, 25*(6), 651-663.

Beck, R., Perkins, T. S., Holder, R., Robbins, M., Gray, M., & Allison, S. H. (2001). The cognitive and emotional phenomenology of depression and anxiety: Are worry and hopelessness the cognitive correlates of NA and PA? *Cognitive Therapy and Research, 25*(6), 829-838.

Beesdo, K., Knappe, S., & Pine, D. S. (2009). Anxiety and anxiety disorders in children and adolescents: developmental issues and implications for DSM-V. *Pediatric Clinics of North America, 32*(3), 483-524.

Beevers, C. G., & Carver, C. S. (2003). Attentional bias and mood persistence as prospective predictors of dysphoria. *Cognitive Therapy and Research, 27*(6), 619-637.

Beevers, C. G., Marti, C. N., Lee, H.-J., Stote, D. L., Ferrell, R. E., Hariri, A. R., & Telch, M. J. (2011). Associations Between Serotonin Transporter Gene Promoter Region (5-HTTLPR) Polymorphism and Gaze Bias for Emotional Information. *Journal of Abnormal Psychology, 120*(1), 187-197. Retrieved from http://www.sciencedirect.com/science/article/pii/S0021843X11600175

Beevers, C. G., Wells, T. T., Ellis, A. J., & McGeary, J. E. (2009). Association of the serotonin transporter gene promoter region (5-HTTLPR) polymorphism with biased attention for emotional stimuli. *Journal of Abnormal Psychology, 118*(3), 670-681. doi:10.1037/a0016198

Beidel, D. C., & Turner, S. M. (1997). At risk for Anxiety: I. Psychopathology in the Offspring of Anxious Parents. *Journal of the American Academic of Child and Adolescent Psychiatry, 36*(7), 918-924.

Benke, K. S., Nivard, M. G., Velders, F. P., Walters, R. K., Pappa, I., Scheet, P. A., . . . Whitehouse, A. J. (2014). A genome-wide association meta-analysis of preschool internalizing problems. *Journal of the American Academy of Child and Adolescent Psychiatry, 53*(6), 667-676. e667.

Bergen-Cico, D., & Cheon, S. (2014). The mediating effects of mindfulness and self-compassion on trait anxiety. *Mindfulness, 5*(5), 505-519.

Bergen, S. E., Gardner, C. O., & Kendler, K. S. (2007). Age-related changes in heritability of behavioral phenotypes over adolescence and young adulthood: a meta-analysis. *Twin Research and Human Genetics, 10*(03), 423-433.

Berman, S. L., Weems, C. F., Silverman, W. K., & Kurtines, W. M. (2000). Predictors of outcome in exposure-based cognitive and behavioral treatments for phobic and anxiety disorders in children. *Behavior Therapy, 31*(4), 713-731.

Bernier, A., Carlson, S. M., Deschênes, M., & Matte-Gagné, C. (2012). Social factors in the development of early executive functioning: a closer look at the caregiving environment. *Developmental Science, 15*(1), 12-24.

Best, J. R., Miller, P. H., & Naglieri, J. A. (2011). Relations between executive function and academic achievement from ages 5 to 17 in a large, representative national sample. *Learning and Individual Differences, 21*(4), 327-336.

Bibok, M. B., Carpendale, J. I., & Müller, U. (2009). Parental scaffolding and the development of executive function. *New Directions for Child and Adolescent Development, 2009*(123), 17-34.

Bienvenu, O. J., Hettema, J. M., Neale, M. C., Prescott, C. A., & Kendler, K. S. (2007). Low extraversion and high neuroticism as indices of genetic and environmental risk for social phobia, agoraphobia, and animal phobia. *American Journal of Psychiatry, 164*(11), 1714-1721.

Birmaher, B., Brent, D. A., Chiappetta, L., Bridge, J., Monga, S., & Baugher, M. (1999). Psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED): a replication study. *Journal of the American Academy of Child and Adolescent Psychiatry, 38*(10), 1230-1236.

Birmaher, B., Ryan, N. D., Williamson, D. E., Brent, D. A., & Kaufman, J. (1996). Childhood and adolescent depression: a review of the past 10 years. Part II. *Journal of the American Academy of Child and Adolescent Psychiatry, 35*, 1575-1583.

Bishop, S. R., Lau, M., Shapiro, S., Carlson, L., Anderson, N. D., Carmody, J., . . . Velting, D. (2004). Mindfulness: A proposed operational definition. *Clinical psychology: Science and practice, 11*(3), 230-241.

Bittner, A., Egger, H. L., Erkanli, A., Costello, E. J., Foley, D. L., & Angold, A. (2007). What do childhood anxiety disorders predict? *Journal of child psychology and psychiatry, 48*(12), 1174-1183. doi:10.1111/j.1469-7610.2007.01812.x

Black, D. S., Sussman, S., Johnson, C. A., & Milam, J. (2012). Psychometric assessment of the mindful attention awareness scale (MAAS) among Chinese adolescents. *Assessment, 19*(1), 42-52.

Blakemore, S.-J. (2008). The social brain in adolescence. *Nature Reviews: Neuroscience, 9*(4), 267-277.

Bogels, S. M., & Brechman-Toussaint, M. L. (2006). Family issues in child anxiety: attachment, family functioning, parental rearing and beliefs. *Clinical psychology review, 26*(7), 834-856.

Boker, S., Neale, M., Maes, H., Wilde, M., Spiegel, M., Brick, T., . . . Bates, T. (2011). OpenMx: an open source extended structural equation modeling framework. *Psychometrika, 76*(2), 306-317.

Bolhuis, K., McAdams, T., Monzani, B., Gregory, A., Mataix-Cols, D., Stringaris, A., & Eley, T. (2014). Aetiological overlap between obsessive–compulsive and depressive symptoms: a longitudinal twin study in adolescents and adults. *Psychological Medicine, 44*(07), 1439-1449.

Boomsma, D. I., Van Beijsterveldt, C. E., Hudziak, J. J., & Van Beijsterveldt, C. E. M. (2005). Genetic and environmental influences on Anxious/Depression during childhood: a study from the Netherlands Twin Register. *Genes, Brain, & Behavior, 4*(8), 466-481. Retrieved from http://www.ingentaconnect.com/content/mksg/gbb/2005/00000004/00000008/art00002

Borkenau, P., Riemann, R., Angleitner, A., & Spinath, F. M. (2002). Similarity of childhood experiences and personality resemblance in monozygotic and dizygotic twins: a test of

the equal environments assumption. *Personality and Individual Differences, 33*(2), 261-269.

Borkovec, T. D., Alcaine, O., & Behar, E. (2004). Avoidance theory of worry and generalized anxiety disorder. *Generalized anxiety disorder: Advances in research and practice, 2004*.

Boswell, J. F., Farchione, T. J., Sauer-Zavala, S., Murray, H. W., Fortune, M. R., & Barlow, D. H. (2013). Anxiety sensitivity and interoceptive exposure: A transdiagnostic construct and change strategy. *Behavior Therapy, 44*(3), 417-431.

Bouchard, T. J., Jr., Lykken, D. T., McGue, M., Segal, N. L., & Tellegen, A. (1990). Sources of human psychological differences: The Minnesota Study of Twins Reared Apart. *science, 250*, 223-228.

Boutwell, B. B., Beaver, K. M., & Barnes, J. (2012). More Alike Than Different Assortative Mating and Antisocial Propensity in Adulthood. *Criminal Justice and Behavior, 39*(9), 1240-1254.

Brady, E. U., & Kendall, P. C. (1992). Comorbidity of anxiety and depression in children and adolescents. *Psychological Bulletin, 111*, 244-255.

Bredemeier, K., & Berenbaum, H. (2013). Cross-sectional and longitudinal relations between working memory performance and worry. *Journal of Experimental Psychopathology, 4*(4), 420-434.

Brewin, C. R. (1996). Theoretical foundations of cognitive-behavior therapy for anxiety and depression. *Annual Review of Psychology, 47*, 33-57.

Brodbeck, J., Abbott, R. A., Goodyer, I. M., & Croudace, T. J. (2011). General and specific components of depression and anxiety in an adolescent population. *BMC psychiatry, 11*(1), 191.

Broeren, S., Muris, P., Bouwmeester, S., van der Heijden, K. B., & Abee, A. (2011). The role of repetitive negative thoughts in the vulnerability for emotional problems in non-clinical children. *Journal of Child and Family Studies, 20*(2), 135-148.

Brooks, S. J., & Kutcher, S. (2001). Diagnosis and measurement of adolescent depression: a review of commonly utilized instruments. *Journal of Child and Adolescent Psychopharmacology, 11*(4), 341-376.

Brothers, B. M., & Andersen, B. L. (2009). Hopelessness as a predictor of depressive symptoms for breast cancer patients coping with recurrence. *Psycho-Oncology, 18*(3), 267-275.

Brown, H., Eley, T., Broeren, S., MacLeod, C., Rinck, M., Hadwin, J., & Lester, K. (2014). Psychometric properties of reaction time based experimental paradigms measuring anxiety-related information-processing biases in children. *Journal of Anxiety Disorders, 28*(1), 97-107.

Brown, H. M., McAdams, T. A., Lester, K. J., Goodman, R., Clark, D. M., & Eley, T. C. (2013). Attentional threat avoidance and familial risk are independently associated with childhood anxiety disorders. *Journal of child psychology and psychiatry, 54*(6), 678-685.

Brown, H. M., Meiser-Stedman, R., Woods, H., & Lester, K. J. (2014). Cognitive Vulnerabilities for Depression and Anxiety in Childhood: Specificity of Anxiety Sensitivity and Rumination. *Behavioural and cognitive psychotherapy*, 1-13.

Brown, H. M., Trzaskowski, M., Zavos, H. M. S., Rijsdijk, F. V., Gregory, A. M., & Eley, T. C. (2012). Phenotypic and genetic structure of anxiety sensitivity in adolescence and early adulthood. *Journal of Anxiety Disorders, 26*(6), 680-688. doi:http://dx.doi.org/10.1016/j.janxdis.2012.05.001

Brown, K. W., & Ryan, R. M. (2003). The benefits of being present: mindfulness and its role in psychological well-being. *Journal of Personality and Social Psychology, 84*(4), 822-848.

Brown, R. A., Lewinsohn, P. M., Seeley, J. R., & Wagner, E. F. (1996). Cigarette smoking, major depression, and other psychiatric disorders among adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry, 35*(12), 1602-1610.

Brown, T. A., Chorpita, B. F., & Barlow, D. H. (1998). Structural relationships among dimensions of the DSM-IV anxiety and mood disorders and dimensions of negative affect, positive affect, and autonomic arousal. *Journal of Abnormal Psychology, 107*(2), 179.

Bruce, S. E., Yonkers, K. A., Otto, M. W., Eisen, J. L., Weisberg, R. B., Pagano, M., . . . Keller, M. B. (2005). Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: a 12-year prospective study. *American Journal of Psychiatry, 162*(6), 1179-1187.

Buchsbaum, B. R., Greer, S., Chang, W. L., & Berman, K. F. (2005). Meta-analysis of neuroimaging studies of the Wisconsin card-sorting task and component processes. *Human Brain Mapping, 25*(1), 35-45.

Burke, C. A. (2010). Mindfulness-based approaches with children and adolescents: A preliminary review of current research in an emergent field. *Journal of Child and Family Studies, 19*(2), 133-144.

Burkhouse, K. L., Siegle, G. J., & Gibb, B. E. (2014). Pupillary reactivity to emotional stimuli in children of depressed and anxious mothers. *Journal of child psychology and psychiatry, 55*(9), 1009-1016.

Burleson Daviss, W., Birmaher, B., Melhem, N. A., Axelson, D. A., Michaels, S. M., & Brent, D. A. (2006). Criterion validity of the Mood and Feelings Questionnaire for depressive episodes in clinic and non-clinic subjects. *Journal of child psychology and psychiatry, 47*(9), 927-934.

Burt, S. A. (2009). Rethinking environmental contributions to child and adolescent psychopathology: a meta-analysis of shared environmental influences. *Psychological Bulletin, 135*(4), 608.

Byrne, A., & Eysenck, M. W. (1995). Trait anxiety, anxious mood, and threat detection. *Cognition & emotion, 9*(6), 549-562.

Calamari, J. E., Hale, L. R., Heffelfinger, S. K., Janeck, A. S., Lau, J. J., Weerts, M. A., . . . Schisler, R. L. (2001). Relations between anxiety sensitivity and panic symptoms in nonreferred children and adolescents. *Journal of Behavior Therapy and Experimental Psychiatry, 32*(3), 117-136.

Callinan, S., Johnson, D., & Wells, A. (2014). A randomised controlled study of the effects of the attention training technique on traumatic stress symptoms, emotional attention set shifting and flexibility. *Cognitive Therapy and Research*, 1-10.

Cannon, M. F., & Weems, C. F. (2006). Do anxiety and depression cluster into distinct groups?: A test of tripartite model predictions in a community sample of youth. *Depression and anxiety, 23*(8), 453-460.

Carballo, J. J., Muñoz-Lorenzo, L., Blasco-Fontecilla, H., Lopez-Castroman, J., García-Nieto, R., Dervic, K., . . . Baca-García, E. (2011). Continuity of depressive disorders from childhood and adolescence to adulthood: a naturalistic study in community mental health centers. *The primary care companion to CNS disorders, 13*(5).

Carleton, R. N. (2012). The intolerance of uncertainty construct in the context of anxiety disorders: Theoretical and practical perspectives.

Carleton, R. N., Fetzner, M. G., Hackl, J. L., & McEvoy, P. (2013). Intolerance of uncertainty as a contributor to fear and avoidance symptoms of panic attacks. *Cognitive Behaviour Therapy, 42*(4), 328-341.

Cartwright-Hatton, S., McNicol, K., & Doubleday, E. (2006). Anxiety in a neglected population: Prevalence of anxiety disorders in pre-adolescent children. *Clinical psychology review, 26*(7), 817-833.

Cash, M., & Whittingham, K. (2010). What facets of mindfulness contribute to psychological well-being and depressive, anxious, and stress-related symptomatology? *Mindfulness, 1*(3), 177-182.

Caspi, A., Houts, R. M., Belsky, D. W., Goldman-Mellor, S. J., Harrington, H., Israel, S., . . . Poulton, R. (2014). The p factor one general psychopathology factor in the structure of psychiatric disorders? *Clinical Psychological Science, 2*(2), 119-137.

Castaneda, A. E., Marttunen, M., Suvisaari, J., Perälä, J., Saarni, S., Aalto-Setälä, T., . . . Tuulio-Henriksson, A. (2010). The effect of psychiatric co-morbidity on cognitive functioning in a population-based sample of depressed young adults. *Psychological Medicine, 40*(1), 29.

Castaneda, A. E., Tuulio-Henriksson, A., Marttunen, M., Suvisaari, J., & Lönnqvist, J. (2008). A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. *Journal of Affective Disorders, 106*(1), 1-27.

Chambers, R., Lo, B. C. Y., & Allen, N. B. (2008). The impact of intensive mindfulness training on attentional control, cognitive style, and affect. *Cognitive Therapy and Research, 32*(3), 303-322.

Chantarujikapong, S. I., Scherrer, J. F., Xian, H., Eisen, S. A., Lyons, M. J., Goldberg, J., . . . True, W. R. (2001). A twin study of generalized anxiety disorder symptoms, panic disorder symptoms and post-traumatic stress disorder in men. *Psychiatry Research, 103*(2), 133-145.

Chelminski, I., & Zimmerman, M. (2003). Pathological worry in depressed and anxious patients. *Journal of Anxiety Disorders, 17*(5), 533-546.

Chen, F. F., Hayes, A., Carver, C. S., Laurenceau, J. P., & Zhang, Z. (2012). Modeling general and specific variance in multifaceted constructs: A comparison of the bifactor model to other approaches. *Journal of Personality, 80*(1), 219-251.

Chen, F. F., West, S. G., & Sousa, K. H. (2006). A comparison of bifactor and second-order models of quality of life. *Multivariate Behavioral Research, 41*(2), 189-225.

Chen, J., & Li, X. (2013). Genetic and environmental influences on adolescent rumination and its association with depressive symptoms. *Journal of Abnormal Child Psychology, 41*(8), 1289-1298.

Chen, J., & Li, X. (2014). Genetic and Environmental Etiologies of Adolescent Dysfunctional Attitudes: A Twin Study. *Twin Research and Human Genetics, 17*(01), 16-22.

Chen, K. W., Berger, C. C., Manheimer, E., Forde, D., Magidson, J., Dachman, L., & Lejuez, C. (2012). Meditative therapies for reducing anxiety: A systematic review and meta-analysis of randomized controlled trials. *Depression and anxiety, 29*(7), 545-562.

Cheung, A., Mayes, T., Levitt, A., Schaffer, A., Michalak, E., Kiss, A., & Emslie, G. (2010). Anxiety as a predictor of treatment outcome in children and adolescents with depression. *Journal of Child and Adolescent Psychopharmacology, 20*(3), 211-216.

Cheyne, J. A., Carriere, J. S., & Smilek, D. (2006). Absent-mindedness: Lapses of conscious awareness and everyday cognitive failures. *Consciousness and Cognition, 15*(3), 578-592.

Chiesa, A., Calati, R., & Serretti, A. (2011). Does mindfulness training improve cognitive abilities? A systematic review of neuropsychological findings. *Clinical psychology review, 31*(3), 449-464.

Chiesa, A., & Serretti, A. (2010). A systematic review of neurobiological and clinical features of mindfulness meditations. *Psychological Medicine, 40*(08), 1239-1252.

Chiesa, A., Serretti, A., & Jakobsen, J. C. (2013). Mindfulness: Top–down or bottom–up emotion regulation strategy? *Clinical psychology review, 33*(1), 82-96.

Chorpita, B. F. (2002). The tripartite model and dimensions of anxiety and depression: An examination of structure in a large school sample. *Journal of Abnormal Child Psychology, 30*(2), 177-190.

Chorpita, B. F., Albano, A. M., & Barlow, A. (1996). Child Anxiety Sensitivity Index: Considerations for Children with Anxiety Disorders. *Journal of Clinical Child Psychology, 25*, 77-82.

Chorpita, B. F., Plummer, C. M., & Moffitt, C. E. (2000). Relations of tripartite dimensions of emotion to childhood anxiety and mood disorders. *Journal of Abnormal Child Psychology, 28*(3), 299-310.

Chorpita, B. F., Yim, L., Moffitt, C., Umemoto, L. A., & Francis, S. E. (2000). Assessment of symptoms of DSM-IV anxiety and depression in children: A revised child anxiety and depression scale. *Behaviour Research and Therapy, 38*(8), 835-855.

Christensen, K., Petersen, I., Skytthe, A., Herskind, A. M., McGue, M., & Bingley, P. (2006). Comparison of academic performance of twins and singletons in adolescence: follow-up study. *British Medical Journal, 333*(7578), 1095.

Chu, B. C., & Harrison, T. L. (2007). Disorder-specific effects of CBT for anxious and depressed youth: a meta-analysis of candidate mediators of change. *Clinical Child and Family Psychology Review, 10*(4), 352-372.

Cisler, J. M., & Koster, E. H. (2010). Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clinical psychology review, 30*(2), 203-216.

Clark, L. A., & Beck, A. T. (1989). Cognitive theory and therapy of anxiety and depression. In P. C. Kendall & D. Watson (Eds.), *Anxiety and depression: Distinctive and overlapping features* (pp. 379-411). San Diego, California: Academic Press.

Clark, L. A., & Watson, D. (1991). Tripartite model of anxiety and depression: Psychometric evidence and taxonomic implications. *J Adnorm Psychol, 100*, 316-336.

Clarke, D., & Currie, K. (2009). Depression, anxiety and their relationship with chronic diseases: a review of the epidemiology, risk and treatment evidence. *The Medical journal of Australia, 190*(7 Suppl), S54.

Cloitre, M., Cancienne, J., Heimberg, R. G., Holt, C. S., & Liebowitz, M. (1995). Memory bias does not generalize across anxiety disorders. *Behaviour Research and Therapy, 33*(3), 305-307.

Cohen-Woods, S., Craig, I., & McGuffin, P. (2013). The current state of play on the molecular genetics of depression. *Psychological Medicine, 43*(04), 673-687.

Cole, D. A., Peeke, L. G., Martin, J. M., Truglio, R., & Seroczynski, A. D. (1998). A longitudinal look at the relation between depression and anxiety in children and adolescents. *Journal of Consulting and Clinical Psychology, 66*(3), 451-460. Retrieved from <Go to ISI>://WOS:000074213200001

Cole, D. A., Truglio, R., & Peeke, L. (1997). Relation between symptoms of anxiety and depression in children: A multitrait-multimethod-multigroup assessment. *Journal of Consulting and Clinical Psychology, 65*(1), 110.

Coles, M. E., & Heimberg, R. G. (2002). Memory biases in the anxiety disorders: Current status. *Clinical psychology review, 22*(4), 587-627.

Conley, D., Rauscher, E., Dawes, C., Magnusson, P. K., & Siegal, M. L. (2013). Heritability and the equal environments assumption: evidence from multiple samples of misclassified twins. *Behavior Genetics, 43*(5), 415-426.

Connolly, S. L., Wagner, C. A., Shapero, B. G., Pendergast, L. L., Abramson, L. Y., & Alloy, L. B. (2014). Rumination prospectively predicts executive functioning impairments in adolescents. *Journal of Behavior Therapy and Experimental Psychiatry, 45*(1), 46-56.

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature reviews neuroscience, 3*(3), 201-215.

Cosgrove, V. E., Rhee, S. H., Gelhorn, H. L., Boeldt, D., Corley, R. C., Ehringer, M. A., . . . Hewitt, J. K. (2011). Structure and etiology of co-occurring internalizing and externalizing disorders in adolescents. *Journal of Abnormal Child Psychology, 39*(1), 109-123.

Costello, E. J., Copeland, W., & Angold, A. (2011). Trends in psychopathology across the adolescent years: What changes when children become adolescents, and when adolescents become adults? *Journal of child psychology and psychiatry, 52*(10), 1015-1025.

Costello, E. J., Mustillo, S., Erkanli, A., Keeler, G., & Angold, A. (2003). Prevalence and development of psychiatric disorders in childhood and adolescence. *Archives of General Psychiatry, 60*(8), 837-844.

Costello, J., Erkanli, A., & Angold, A. (2006). Is there an epidemic of child or adolescent depression? *Journal of child psychology and psychiatry, 47*(12), 1263-1271.

Creswell, C., & O'Connor, T. G. (2011). Interpretation bias and anxiety in childhood: Stability, specificity and longitudinal associations. *Behavioural and cognitive psychotherapy, 39*(02), 191-204.

Creswell, J. D., Way, B. M., Eisenberger, N. I., & Lieberman, M. D. (2007). Neural correlates of dispositional mindfulness during affect labeling. *Psychosomatic Medicine, 69*(6), 560-565.

Cristea, I. A., Mogoașe, C., David, D., & Cuijpers, P. (2015). Practitioner review: cognitive bias modification for mental health problems in children and adolescents: a meta-analysis. *Journal of child psychology and psychiatry*.

Crocker, L. D., Heller, W., Warren, S. L., O'Hare, A. J., Infantolino, Z. P., & Miller, G. A. (2013). Relationships among cognition, emotion, and motivation: implications for intervention and neuroplasticity in psychopathology. *Frontiers in human neuroscience, 7*.

Cronk, N. J., Slutske, W. S., Madden, P. A., Bucholz, K. K., Reich, W., & Heath, A. C. (2002). Emotional and behavioral problems among female twins: an evaluation of the equal environments assumption. *Journal of American Academic Child and Adolescent Psychiatry, 41*(7), 829-837.

Cross-Disorder Group of the Psychiatric Genomics Consortium. (2013). Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nature Genetics, 45*(9), 984-994.

Cummings, C. M., Caporino, N. E., & Kendall, P. C. (2014). Comorbidity of anxiety and depression in children and adolescents: 20 years after. *Psychological Bulletin, 140*(3), 816.

Cummings, C. M., & Fristad, M. A. (2012). Anxiety in children with mood disorders: A treatment help or hindrance? *Journal of Abnormal Child Psychology, 40*(3), 339-351.

Curry, J., Rohde, P., Simons, A., Silva, S., Vitiello, B., Kratochvil, C., . . . Pathak, S. (2006). Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS). *Journal of the American Academy of Child and Adolescent Psychiatry, 45*(12), 1427-1439.

Czajkowski, N., Kendler, K., Tambs, K., Røysamb, E., & Reichborn-Kjennerud, T. (2011). The structure of genetic and environmental risk factors for phobias in women. *Psychological Medicine, 41*(09), 1987-1995.

Dadds, M. R., Barrett, P. M., Rapee, R. M., & Ryan, S. (1996). Family process and child anxiety and aggression: an observational analysis. *Journal of Abnormal.Child Psychology, 24*(6), 715-734.

Dalgleish, T., Taghavi, R., Neshat-Doost, H., Moradi, A., Canterbury, R., & Yule, W. (2003). Patterns of processing bias for emotional information across clinical disorders: a comparison of attention, memory, and prospective cognition in children and adolescents with depression, generalized anxiety, and posttraumatic stress disorder. *Journal of Clinical Child & Adolescent Psychology, 32*(1), 10-21.

Davidson, J. R., Tupler, L. A., Wilson, W. H., & Connor, K. M. (1998). A family study of chronic post-traumatic stress disorder following rape trauma. *Journal of Psychiatric Research, 32*(5), 301-309.

Davidson, R. J. (2010). Empirical explorations of mindfulness: conceptual and methodological conundrums. *Emotion, 10*(1), 8-11.

Davis, R. N., & Nolen-Hoeksema, S. (2000). Cognitive inflexibility among ruminators and nonruminators. *Cognitive Therapy and Research, 24*(6), 699-711.

De Lissnyder, E., Koster, E. H., Goubert, L., Onraedt, T., Vanderhasselt, M.-A., & De Raedt, R. (2012). Cognitive control moderates the association between stress and rumination. *Journal of Behavior Therapy and Experimental Psychiatry, 43*(1), 519-525.

De Raedt, R., Baert, S., Demeyer, I., Goeleven, E., Raes, A., Visser, A., . . . Van Aalderen, J. R. (2012). Changes in attentional processing of emotional information following mindfulness-based cognitive therapy in people with a history of depression: Towards an open attention for all emotional experiences. *Cognitive Therapy and Research, 36*(6), 612-620.

Dearing, K., & Gotlib, I. (2009). Interpretation of Ambiguous Information in Girls at Risk for Depression. *Journal of Abnormal Child Psychology, 37*(1), 79-91. doi:10.1007/s10802-008-9259-z

Dehon, C., Weems, C. F., Stickle, T. R., Costa, N. M., & Berman, S. L. (2005). A cross-sectional evaluation of the factorial invariance of anxiety sensitivity in adolescents and young adults. *Behaviour Research and Therapy, 43*(6), 799-810.

Dekeyser, M., Raes, F., Leijssen, M., Leysen, S., & Dewulf, D. (2008). Mindfulness skills and interpersonal behaviour. *Personality and Individual Differences, 44*(5), 1235-1245.

Delgado, L. C., Guerra, P., Perakakis, P., Vera, M. N., del Paso, G. R., & Vila, J. (2010). Treating chronic worry: Psychological and physiological effects of a training programme based on mindfulness. *Behaviour Research and Therapy, 48*(9), 873-882.

Demirkan, A., Penninx, B. W., Hek, K., Wray, N. R., Amin, N., Aulchenko, Y. S., . . . Uitterlinden, A. G. (2011). Genetic risk profiles for depression and anxiety in adult and elderly cohorts. *Molecular Psychiatry, 16*(7), 773-783.

Derakshan, N., & Eysenck, M. W. (2009). Anxiety, processing efficiency, and cognitive performance. *European Psychologist, 14*(2), 168-176.

Derakshan, N., Smyth, S., & Eysenck, M. W. (2009). Effects of state anxiety on performance using a task-switching paradigm: An investigation of attentional control theory. *Psychonomic bulletin & review, 16*(6), 1112-1117.

Derryberry, D., & Reed, M. A. (2002). Anxiety-related attentional biases and their regulation by attentional control. *Journal of Abnormal Psychology, 111*(2), 225-236.

Desrosiers, A., Klemanski, D. H., & Nolen-Hoeksema, S. (2013). Mapping mindfulness facets onto dimensions of anxiety and depression. *Behavior Therapy, 44*(3), 373-384.

Desrosiers, A., Vine, V., Klemanski, D. H., & Nolen-Hoeksema, S. (2013). Mindfulness and emotion regulation in depression and anxiety: common and distinct mechanisms of action. *Depression and anxiety, 30*(7), 654-661.

Dieleman, G. C., Van der Ende, J., Verhulst, F. C., & Huizink, A. C. (2010). Perceived and physiological arousal during a stress task: Can they differentiate between anxiety and depression? *Psychoneuroendocrinology, 35*(8), 1223-1234.

Dineen, K. A., & Hadwin, J. A. (2004). Anxious and depressive symptoms and children's judgements of their own and others' interpretation of ambiguous social scenarios. *Journal of Anxiety Disorders, 18*(4), 499-513.

Dodd, H. F., Hudson, J. L., Morris, T. M., & Wise, C. K. (2012). Interpretation bias in preschool children at risk for anxiety: a prospective study. *Journal of Abnormal Psychology, 121*(1), 28.

Dodd, H. F., Stuijfzand, S., Morris, T., & Hudson, J. L. (2015). Child Anxiety and the Processing of Ambiguity. *Cognitive Therapy and Research*, 1-9.

Dube, J., Dodds, L., & Armson, B. A. (2002). Does chorionicity or zygosity predict adverse perinatal outcomes in twins? *American Journal of Obstetrics and Gynecology, 186*(3), 579-583.

Dunn, V., & Goodyer, I. M. (2006). Longitudinal investigation into childhood-and adolescence-onset depression: psychiatric outcome in early adulthood. *The British Journal of Psychiatry, 188*(3), 216-222.

Eaton, N. R., Krueger, R. F., Markon, K. E., Keyes, K. M., Skodol, A. E., Wall, M., . . . Grant, B. F. (2013). The structure and predictive validity of the internalizing disorders. *Journal of Abnormal Psychology, 122*(1), 86-92.

Eaton, N. R., Krueger, R. F., & Oltmanns, T. F. (2011). Aging and the structure and long-term stability of the internalizing spectrum of personality and psychopathology. *Psychology and Aging, 26*(4), 987-993.

Eaves, L. J., D'Onofrio, B., & Russell, R. (1999). Transmission of religion and attitudes. *Twin Research, 2*, 59-61.

Eberth, J., & Sedlmeier, P. (2012). The effects of mindfulness meditation: a meta-analysis. *Mindfulness, 3*(3), 174-189.

Eide, P., Kemp, A., Silberstein, R., Nathan, P., & Stough, C. (2002). Test-retest reliability of the emotional Stroop task: Examining the paradox of measurement change. *The Journal of Psychology, 136*(5), 514-520.

Eisenberg, N., Cumberland, A., Spinrad, T. L., Fabes, R. A., Shepard, S. A., Reiser, M., . . . Guthrie, I. K. (2001). The relations of regulation and emotionality to children's externalizing and internalizing problem behavior. *Child Development, 72*(4), 1112-1134.

Eizenman, M., Lawrence, H. Y., Grupp, L., Eizenman, E., Ellenbogen, M., Gemar, M., & Levitan, R. D. (2003). A naturalistic visual scanning approach to assess selective attention in major depressive disorder. *Psychiatry Research, 118*(2), 117-128.

Ekornas, B., Lundervold, A. J., Tjus, T., & Heimann, M. (2010). Anxiety disorders in 8–11-year-old children: Motor skill performance and self-perception of competence. *Scandinavian Journal of Psychology, 51*(3), 271-277.

Eley, T. C. (1997). General genes: A new theme in developmental psychopathology. *Current Directions in Psychological Science, 6*, 90-95.

Eley, T. C., Bolton, D., O'Connor, T. G., Perrin, S., Smith, P., & Plomin, R. (2003). A twin study of anxiety-related behaviours in pre-school children. *Journal of child psychology and psychiatry, 44*(7), 945-960.

Eley, T. C., Collier, D., McGuffin, P., Owen, M. J., & Gottesman, I. I. (2002). Anxiety and eating disorders *Psychiatric Genetics & Genomics* (pp. 303-340). Oxford: Oxford University Press.

Eley, T. C., Gregory, A. M., Clark, D. M., & Ehlers, A. (2007). Feeling anxious: A twin study of panic/somatic symptoms, anxiety sensitivity and heart-beat perception in children. *Journal of child psychology and psychiatry, 48*(12), 1184-1191.

Eley, T. C., Gregory, A. M., Lau, J. Y. F., McGuffin, P., Napolitano, M., Rijsdijk, F. V., & Clark, D. M. (2008). In the face of uncertainty: A genetic analysis of ambiguous information, anxiety and depression in children. *Journal of Abnormal Child Psychology, 48*(12), 55-65. Retrieved from Online early DOI: 10.1007/s10802-007-9159-7.

Eley, T. C., Hudson, J. L., Creswell, C., Tropeano, M., Lester, K. J., Cooper, P., . . . Collier, D. A. (2012). Therapygenetics: the 5HTTLPR and response to psychological therapy. *Molecular Psychiatry, 17*(3), 236-237. Retrieved from http://dx.doi.org/10.1038/mp.2011.132

http://www.nature.com/mp/journal/v17/n3/suppinfo/mp2011132s1.html

Eley, T. C., Rijsdijk, F. V., Perrin, S., O'Connor, T. G., & Bolton, D. (2008). A Multivariate Genetic Analysis of Specific Phobia, Separation Anxiety and Social Phobia in Early Childhood. *Journal of Abnormal Child Psychology, 36*(6), 839-848. Retrieved from Online early DOI: 10.1007/s10802-008-9216-x.

Eley, T. C., & Stevenson, J. (1999). Using genetic analyses to clarify the distinction between depressive and anxious symptoms in children and adolescents. *Journal of Abnormal Child Psychology, 27*(2), 105-114.

Eley, T. C., & Stevenson, J. (2000). Specific life events and chronic experiences differentially associated with depression and anxiety in young twins. *Journal of Abnormal Child Psychology, 28*(4), 383-394.

Emck, C., Bosscher, R. J., Van Wieringen, P. C., Doreleijers, T., & Beek, P. J. (2011). Gross motor performance and physical fitness in children with psychiatric disorders. *Developmental Medicine and Child Neurology, 53*(2), 150-155.

Epkins, C. C., Gardner, C., & Scanlon, N. (2013). Rumination and anxiety sensitivity in preadolescent girls: Independent, combined, and specific associations with depressive and anxiety symptoms. *Journal of Psychopathology and Behavioral Assessment, 35*(4), 540-551.

Essau, C. A., Conradt, J., & Petermann, F. (2000). Frequency, comorbidity, and psychosocial impairment of anxiety disorders in German adolescents. *Journal of Anxiety Disorders, 14*(3), 263-279.

Esterman, M., DeGutis, J., Mercado, R., Rosenblatt, A., Vasterling, J. J., Milberg, W., & McGlinchey, R. (2013). Stress-related psychological symptoms are associated with increased attentional capture by visually salient distractors. *Journal of the International Neuropsychological Society, 19*(07), 835-840.

Eysenck, M. W., & Derakshan, N. (2011). New perspectives in attentional control theory. *Personality and Individual Differences, 50*(7), 955-960.

Eysenck, M. W., Derakshan, N., Santos, R., & Calvo, M. G. (2007). Anxiety and cognitive performance: attentional control theory. *Emotion, 7*(2), 336-353.

Farchione, T. J., Fairholme, C. P., Ellard, K. K., Boisseau, C. L., Thompson-Hollands, J., Carl, J. R., . . . Barlow, D. H. (2012). Unified protocol for transdiagnostic treatment of emotional disorders: a randomized controlled trial. *Behavior Therapy, 43*(3), 666-678.

Felson, J. (2014). What can we learn from twin studies? A comprehensive evaluation of the equal environments assumption. *Social Science Research, 43*, 184-199.

Ferdinand, R. F., Dieleman, G., Ormel, J., & Verhulst, F. C. (2007). Homotypic versus heterotypic continuity of anxiety symptoms in young adolescents: evidence for distinctions between DSM-IV subtypes. *Journal of Abnormal Child Psychology, 35*(3), 325-333.

Fergusson, D. M., Horwood, L. J., & Boden, J. M. (2006). Structure of internalising symptoms in early adulthood. *The British Journal of Psychiatry, 189*(6), 540-546.

Fergusson, D. M., Horwood, L. J., Ridder, E. M., & Beautrais, A. L. (2005). Subthreshold depression in adolescence and mental health outcomes in adulthood. *Archives of General Psychiatry, 62*(1), 66-72.

Feske, U., & Chambless, D. L. (1995). Cognitive behavioral versus exposure only treatment for social phobia: A meta-analysis. *Behavior Therapy, 26*(4), 695-720.

Field, A. P. (2006). Watch out for the beast: Fear information and attentional bias in children. *Journal of Clinical Child and Adolescent Psychology, 35*(3), 431-439.

Field, A. P., & Lester, K. J. (2010). Is There Room for 'Development' in Developmental Models of Information Processing Biases to Threat in Children and Adolescents? *Clinical Child and Family Psychology Review, 13*(4), 315-332. doi:10.1007/s10567-010-0078-8

Finch Jr, A., Montgomery, L., & Deardorff, P. (1974). Reliability of state-trait anxiety with emotionally disturbed children. *Journal of Abnormal Child Psychology, 2*(1), 67-69.

Finlay-Jones, R., & Brown, G. W. (1981). Types of stressful life events and the onset of anxiety and depressive disorders. *Psychological Medicine, 11*, 803-815.

Flint, J., & Kendler, K. S. (2014). The genetics of major depression. *Neuron, 81*(3), 484-503.

Ford, T., Goodman, R., & Meltzer, H. (2003). The British Child and Adolescent Mental Health Survey 1999: the prevalence of DSM-IV disorders. *Journal of the American Academy of Child & Adolescent Psychiatry.42(10):1203-11*.

Fox, E., Ridgewell, A., & Ashwin, C. (2009). Looking on the bright side: biased attention and the human serotonin transporter gene. *Proceedings of the Royal Society B: Biological Sciences*, rspb. 2008.1788.

Franic, S., Middeldorp, C. M., Dolan, C. V., Ligthart, L., & Boomsma, D. I. (2010). Childhood and Adolescent Anxiety and Depression: Beyond Heritability. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(8), 820-829. doi:10.1016/j.jaac.2010.05.013

French, C. C., & Richards, A. (1992). Word association norms for a set of threat/neutral homographs. *Cognition & emotion, 6*(1), 65-87.

Fresco, D. M., Frankel, A. N., Mennin, D. S., Turk, C. L., & Heimberg, R. G. (2002). Distinct and overlapping features of rumination and worry: The relationship of cognitive production to negative affective states. *Cognitive Therapy and Research, 26*(2), 179-188.

Friedman, N. P., Miyake, A., Young, S. E., DeFries, J. C., Corley, R. P., & Hewitt, J. K. (2008). Individual differences in executive functions are almost entirely genetic in origin. *Journal of Experimental Psychology: General, 137*(2), 201.

Frodl, T., Schaub, A., Banac, S., Charypar, M., Jäger, M., Kümmler, P., . . . Leinsinger, G. (2006). Reduced hippocampal volume correlates with executive dysfunctioning in major depression. *Journal of Psychiatry and Neuroscience, 31*(5), 316.

Garcia, S. E., Tully, E. C., Tarantino, N., South, S., Iacono, W. G., & McGue, M. (2013). Changes in genetic and environmental influences on trait anxiety from middle adolescence to early adulthood. *Journal of Affective Disorders, 151*(1), 46-53.

Gazelle, H., & Ladd, G. W. (2003). Anxious solitude and peer exclusion: A diathesis–stress model of internalizing trajectories in childhood. *Child Development, 74*(1), 257-278.

Geller, D. A., Biederman, J., Stewart, S. E., Mullin, B., Farrell, C., Wagner, K. D., . . . Carpenter, D. (2003). Impact of comorbidity on treatment response to paroxetine in pediatric obsessive-compulsive disorder: is the use of exclusion criteria empirically supported in randomized clinical trials? *Journal of Child and Adolescent Psychopharmacology, 13*(2, Supplement 1), 19-29.

Gentes, E. L., & Ruscio, A. M. (2011). A meta-analysis of the relation of intolerance of uncertainty to symptoms of generalized anxiety disorder, major depressive disorder, and obsessive–compulsive disorder. *Clinical psychology review, 31*(6), 923-933.

Gibb, B. E., Beevers, C. G., & McGeary, J. E. (2013). Toward an integration of cognitive and genetic models of risk for depression. *Cognition & emotion, 27*(2), 193-216.

Gibb, B. E., Benas, J. S., Grassia, M., & McGeary, J. (2009). Children's Attentional Biases and 5-HTTLPR Genotype: Potential Mechanisms Linking Mother and Child Depression. *Journal of Clinical Child and Adolescent Psychology, 38*(3), 415-426. doi:10.1080/15374410902851705

Gilboa-Schechtman, E., Foa, E. B., & Amir, N. (1999). Attentional biases for facial expressions in social phobia: The face-in-the-crowd paradigm. *Cognition & emotion, 13*(3), 305-318.

Gillespie, N. A., Kirk, K. M., Evans, D. M., Heath, A. C., Hickie, I. B., & Martin, N. G. (2004). Do the genetic or environmental determinants of anxiety and depression change with age? A longitudinal study of Australian twins. *Twin Research, 7*(01), 39-53.

Giluk, T. L. (2009). Mindfulness, Big Five personality, and affect: A meta-analysis. *Personality and Individual Differences, 47*(8), 805-811.

Gladstone, T. R., & Kaslow, N. J. (1995). Depression and attributions in children and adolescents: a meta-analytic review. *Journal of Abnormal Child Psychology., 23*(5), 597-606.

Goenjian, A. K., Walling, D., Steinberg, A. M., Karayan, I., Najarian, L. M., & Pynoos, R. (2005). A prospective study of posttraumatic stress and depressive reactions among treated and

untreated adolescents 5 years after a catastrophic disaster. *American Journal of Psychiatry, 162*(12), 2302-2308.

Goes, F. S., McCusker, M. G., Bienvenu, O. J., MacKinnon, D. F., Mondimore, F. M., Schweizer, B., . . . Potash, J. B. (2012). Co-morbid anxiety disorders in bipolar disorder and major depression: familial aggregation and clinical characteristics of co-morbid panic disorder, social phobia, specific phobia and obsessive-compulsive disorder. *Psychological Medicine, 42*(07), 1449-1459. doi:doi:10.1017/S0033291711002637

Goldberg, D., Krueger, R., Andrews, G., & Hobbs, M. (2009). Emotional disorders: cluster 4 of the proposed meta-structure for DSM-V and ICD-11. *Psychological Medicine, 39*(12), 2043-2059.

Goldin, A. P., Hermida, M. J., Shalom, D. E., Costa, M. E., Lopez-Rosenfeld, M., Segretin, M. S., . . . Sigman, M. (2014). Far transfer to language and math of a short software-based gaming intervention. *Proceedings of the National Academy of Sciences, 111*(17), 6443-6448.

Goldsmith, H. H. (1991). A zygosity questionnaire for young twins: A research note. *Behavior Genetics, 21*(3), 257-269.

Gomez, R., Vance, A., & Gomez, R. M. (2013). The factor structure of anxiety and depressive disorders in a sample of clinic-referred adolescents. *Journal of Abnormal Child Psychology*, 1-12.

Gorlin, E. I., & Teachman, B. A. (2014). Inhibitory control as a moderator of threat-related interference biases in social anxiety. *Cognition and Emotion*(ahead-of-print), 1-13.

Goschke, T. (2014). Dysfunctions of decision-making and cognitive control as transdiagnostic mechanisms of mental disorders: advances, gaps, and needs in current research. *International Journal of Methods in Psychiatric Research, 23*(S1), 41-57.

Gotlib, I. H., & Joormann, J. (2010). Cognition and depression: current status and future directions. *Annual Review of Clinical Psychology, 6*, 285.

Gotlib, I. H., Kasch, K. L., Traill, S., Joormann, J., Arnow, B. A., & Johnson, S. L. (2004). Coherence and specificity of information-processing biases in depression and social phobia. *Journal of Abnormal Psychology, 113*(3), 386-398.

Grant, B. F., Stinson, F. S., Dawson, D. A., Chou, S. P., Dufour, M. C., Compton, W., . . . Kaplan, K. (2004). Prevalence and co-occurrence of substance use disorders and independentmood and anxiety disorders: Results from the national epidemiologic survey on alcohol and relatedconditions. *Archives of General Psychiatry, 61*(8), 807-816.

Grant, D. M., Beck, J. G., & Davila, J. (2007). Does anxiety sensitivity predict symptoms of panic, depression, and social anxiety? *Behaviour Research and Therapy, 45*(9), 2247-2255.

Grant, D. M., Gayle Beck, J., Farrow, S. M., & Davila, J. (2007). Do interpersonal features of social anxiety influence the development of depressive symptoms? *Cognition and Emotion, 21*(3), 646-663.

Greaves-Lord, K., Ferdinand, R. F., Sondeijker, F. E., Dietrich, A., Oldehinkel, A. J., Rosmalen, J. G., . . . Verhulst, F. C. (2007). Testing the tripartite model in young adolescents: Is hyperarousal specific for anxiety and not depression? *Journal of Affective Disorders, 102*(1), 55-63.

Gregory, A. M., Caspi, A., Moffitt, T. E., Koenen, K., Eley, T. C., & Poulton, R. (2007). Juvenile mental health histories of adults with anxiety disorders. *American Journal of Psychiatry, 164*(2), 301-308.

Gregory, A. M., & Eley, T. C. (2009). In W. K. Silverman & A. P. Field (Eds.), *Anxiety Disorders in Children and Adolescents: Research, Assessment and Intervention*. Cambridge: Cambridge University Press.

Gregory, A. M., Rijsdijk, F. V., & Eley, T. C. (2006). A twin-study of sleep difficulties in school-aged children. *Child Development, 77*(6), 1668-1679.

Griffith, J. W., Zinbarg, R. E., Craske, M. G., Mineka, S., Rose, R. D., Waters, A. M., & Sutton, J. M. (2010). Neuroticism as a common dimension in the internalizing disorders. *Psychological Medicine, 40*(07), 1125-1136.

Gros, D. F., McCabe, R. E., & Antony, M. M. (2013). Using a hybrid model to investigate the comorbidity and symptom overlap between social phobia and the other anxiety disorders and unipolar mood disorders. *Psychiatry Research, 210*(1), 188-192.

Gross, J. J. (1998). The emerging field of emotion regulation: an integrative review. *Review of general psychology, 2*(3), 271.

Grossman, P. (2011). Defining mindfulness by how poorly I think I pay attention during everyday awareness and other intractable problems for psychology's (re) invention of mindfulness: comment on Brown et al.(2011). *Psychological Assessment, 23*(4), 1034-1040.

Gu, J., Strauss, C., Bond, R., & Cavanagh, K. (2015). How do mindfulness-based cognitive Therapy and mindfulness-based stress reduction improve mental health and wellbeing? A systematic review and meta-analysis of mediation studies. *Clinical psychology review, 37*, 1-12.

Haddad, A. D. M., Lissek, S., Pine, D. S., & Lau, J. Y. F. (2011). How do social fears in adolescence develop? Fear conditioning shapes attention orienting to social threat cues. *Cognition & emotion, 25*(6), 1139-1147.

Hadwin, A. J., & Field, A. P. (2010). *Information processing biases and anxiety: A developmental perspective*. Chichester: Wiley-Blackwell.

Hadwin, J., Frost, S., French, C., & Richards, A. (1997). Cognitive Processing and Trait Anxiety in Typically Developing Children: Evidence for an Interpretation Bias. *Journal of Abnormal Psychology, 106*(3), 486-490.

Hadwin, J. A., Donnelly, N., French, C. C., Richards, A., Watts, A., & Daley, D. (2003). The influence of children's self-report trait anxiety and depression on visual search for

emotional faces. *Journal of Child Psychology & Psychiatry & Allied Disciplines., 44*(3), 432-444.

Hakamata, Y., Lissek, S., Bar-Haim, Y., Britton, J. C., Fox, N. A., Leibenluft, E., . . . Pine, D. S. (2010). Attention bias modification treatment: a meta-analysis toward the establishment of novel treatment for anxiety. *Biological Psychiatry, 68*(11), 982-990.

Hall, J. G. (2003). Twinning. *The Lancet, 362*(9385), 735-743.

Hallett, V., Ronald, A., Rijsdijk, F. V., & Eley, T. C. (2009). Phenotypic and genetic differentiation of anxiety-related behaviors in middle childhood. *Depression and anxiety, 26*(4), 316-324.

Hallion, L. S., & Ruscio, A. M. (2011). A meta-analysis of the effect of cognitive bias modification on anxiety and depression. *Psychological Bulletin, 137*(6), 940-958. Retrieved from 10.1037/a0024355

http://search.ebscohost.com/login.aspx?direct=true&db=pdh&AN=bul-137-6-940&site=ehost-live

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Hammar, Å., & Årdal, G. (2009). Cognitive functioning in major depression–a summary. *Frontiers in human neuroscience, 3*.

Hammar, Å., Sorensen, L., Årdal, G., Oedegaard, K. J., Kroken, R., Roness, A., & Lund, A. (2010). Enduring cognitive dysfunction in unipolar major depression: a test–retest study using the Stroop paradigm. *Scandinavian Journal of Psychology, 51*(4), 304-308.

Hankin, B. L. (2008). Rumination and depression in adolescence: Investigating symptom specificity in a multiwave prospective study. *Journal of Clinical Child & Adolescent Psychology, 37*(4), 701-713.

Hankin, B. L., & Abramson, L. Y. (2001). Development of gender differences in depression: an elaborated cognitive vulnerability-transactional stress theory. *Psychological Bulletin, 127*(6), 773-796.

Hankin, B. L., Abramson, L. Y., & Siler, M. (2001). A prospective test of the hopelessness theory of depression in adolescence. *Cognitive Therapy and Research, 25*(5), 607-632.

Hankin, B. L., Gibb, B. E., Abela, J. R., & Flory, K. (2010). Selective attention to affective stimuli and clinical depression among youths: role of anxiety and specificity of emotion. *Journal of Abnormal Psychology, 119*(3), 491.

Hansell, N., Wright, M., Medland, S., Davenport, T., Wray, N., Martin, N., & Hickie, I. (2012). Genetic co-morbidity between neuroticism, anxiety/depression and somatic distress in a population sample of adolescent and young adult twins. *Psychological Medicine, 42*(06), 1249-1260.

Happonen, M., Pulkkinen, L., Kaprio, J., Van der Meere, J., Viken, R. J., & Rose, R. J. (2002). The heritability of depressive symptoms: Multiple informants and multiple measures. *Journal of child psychology and psychiatry, 43*(4), 471-479.

Harrington, R., Fudge, H., Rutter, M., Pickles, A., & Hill, J. (1990). Adult outcomes of childhood and adolescent depression. *Archives of General Psychiatry, 47*, 465-473.

Harrington, R., Rutter, M., & Fombonne, E. (1996). Developmental pathways in depression: Multiple meanings, antecedents, and endpoints. *Development and Psychopathology, 8*, 601-616.

Harris, E. C., & Barraclough, B. (1997). Suicide as an outcome for mental disorders. A meta-analysis. *The British Journal of Psychiatry, 170*(3), 205-228.

Harvey, P.-O., Fossati, P., Pochon, J.-B., Levy, R., LeBastard, G., Lehéricy, S., . . . Dubois, B. (2005). Cognitive control and brain resources in major depression: an fMRI study using the n-back task. *Neuroimage, 26*(3), 860-869.

Harvey, P., Le Bastard, G., Pochon, J., Levy, R., Allilaire, J., Dubois, B., & Fossati, P. (2004). Executive functions and updating of the contents of working memory in unipolar depression. *Journal of Psychiatric Research, 38*(6), 567-576.

Haworth, C. M. A., Davis, O. S. P., & Plomin, R. (2013). Twins Early Development Study (TEDS): a genetically sensitive investigation of cognitive and behavioral development from childhood to young adulthood. *Twin Research & Human Genetics, 16*(1), 117-125.

Hazen, A. L., Walker, J. R., & Stein, M. B. (1994). Comparison of anxiety sensitivity in panic disorder and social phobia. *Anxiety, 1*(6), 298-301.

Hendriks, S. M., Licht, C. M., Spijker, J., Beekman, A. T., Hardeveld, F., de Graaf, R., & Penninx, B. W. (2014). Disorder-specific cognitive profiles in major depressive disorder and generalized anxiety disorder. *BMC psychiatry, 14*(1), 96.

Hensley, L., & Varela, R. E. (2008). PTSD Symptoms and Somatic Complaints Following Hurricane Katrina: The Roles of Trait Anxiety and Anxiety Sensitivity. *Journal of Clinical Child & Adolescent Psychology, 37*(3), 542-552. doi:10.1080/15374410802148186

Hettema, J., Chen, X., Sun, C., & Brown, T. (2015). Direct, indirect and pleiotropic effects of candidate genes on internalizing disorder psychopathology. *Psychological Medicine*, 1-10.

Hettema, J. M. (2008a). The nosologic relationship between generalized anxiety disorder and major depression. *Depression and anxiety, 25*(4), 300-316.

Hettema, J. M. (2008b). What is the genetic relationship between anxiety and depression? *American Journal of Medical Genetics Part C: Seminars in Medical Genetics, 148C*, 140-146.

Hettema, J. M., Neale, M. C., & Kendler, K. S. (2001). A Review and Meta-Analysis of the Genetic Epidemiology of Anxiety Disorders. *American Journal of Psychiatry, 158*(10), 1568-1578. Retrieved from http://ajp.psychiatryonline.org/cgi/content/abstract/158/10/1568

Hettema, J. M., Neale, M. C., Myers, J. M., Prescott, C. A., & Kendler, K. S. (2006). A population-based twin study of the relationship between neuroticism and internalizing disorders.

American Journal of Psychiatry, 163(5), 857-864. Retrieved from http://ajp.psychiatryonline.org/cgi/reprint/163/5/857

Hettema, J. M., Prescott, C. A., Myers, J. M., Neale, M. C., & Kendler, K. S. (2005). The structure of genetic and environmental risk factors for anxiety disorders in men and women. *Archives of General Psychiatry, 62*(2), 182-189. Retrieved from http://archpsyc.ama-assn.org/cgi/reprint/62/2/182

Hill, E. L., & Brown, D. (2013). Mood impairments in adults previously diagnosed with developmental coordination disorder. *Journal of Mental Health, 22*(4), 334-340.

Hilt, L. M., Sander, L. C., Nolen-Hoeksema, S., & Simen, A. A. (2007). The BDNF Val66Met polymorphism predicts rumination and depression differently in young adolescent girls and their mothers. *Neuroscience Letters, 429*(1), 12-16.

Hilton, R. C., Rengasamy, M., Mansoor, B., He, J., Mayes, T., Emslie, G. J., . . . Birmaher, B. (2013). Impact of Treatments for Depression on Comorbid Anxiety, Attentional, and Behavioral Symptoms in Adolescents With Selective Serotonin Reuptake Inhibitor–Resistant Depression. *Journal of the American Academy of Child and Adolescent Psychiatry, 52*(5), 482-492.

Hofmann, S. G. (2007). Cognitive factors that maintain social anxiety disorder: A comprehensive model and its treatment implications. *Cognitive Behaviour Therapy, 36*(4), 193-209.

Hofmann, S. G., Sawyer, A. T., Witt, A. A., & Oh, D. (2010). The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. *Journal of Consulting and Clinical Psychology, 78*(2), 169-183. Retrieved from 10.1037/a0018555 http://search.ebscohost.com/login.aspx?direct=true&db=pdh&AN=ccp-78-2-169&site=ehost-live

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Holaway, R. M., Heimberg, R. G., & Coles, M. E. (2006). A comparison of intolerance of uncertainty in analogue obsessive-compulsive disorder and generalized anxiety disorder. *Journal of Anxiety Disorders, 20*(2), 158-174.

Homberg, J. R., & Lesch, K.-P. (2011). Looking on the bright side of serotonin transporter gene variation. *Biological Psychiatry, 69*(6), 513-519.

Hoorelbeke, K., Koster, E. H., Vanderhasselt, M.-A., Callewaert, S., & Demeyer, I. (2015). The influence of cognitive control training on stress reactivity and rumination in response to a lab stressor and naturalistic stress. *Behaviour Research and Therapy, 69*, 1-10.

Hudson, J. I., Mangweth, B., Pope Jr, H. G., De Col, C., Hausmann, A., Gutweniger, S., . . . Tsuang, M. T. (2003). Family study of affective spectrum disorder. *Archives of General Psychiatry, 60*(2), 170-177.

Hudson, J. I., & Pope, H. G. (1990). Affective spectrum disorder: does antidepressant response identify a family of disorders with a common pathophysiology? *The American journal of psychiatry*.

Hughes, C. (2011). Changes and challenges in 20 years of research into the development of executive functions. *Infant and Child Development, 20*(3), 251-271.

Hughes, C., & Ensor, R. (2011). Individual differences in growth in executive function across the transition to school predict externalizing and internalizing behaviors and self-perceived academic success at 6 years of age. *Journal of Experimental Child Psychology, 108*(3), 663-676.

Hyde, J. S., Mezulis, A. H., & Abramson, L. Y. (2008). The ABCs of depression: integrating affective, biological, and cognitive models to explain the emergence of the gender difference in depression. *Psychological Review, 115*(2), 291.

Jacobs, R. H., Reinecke, M. A., Gollan, J. K., & Kane, P. (2008). Empirical evidence of cognitive vulnerability for depression among children and adolescents: A cognitive science and developmental perspective. *Clinical psychology review, 28*(5), 759-782.

Jaeger, J., Berns, S., Uzelac, S., & Davis-Conway, S. (2006). Neurocognitive deficits and disability in major depressive disorder. *Psychiatry Research, 145*(1), 39-48.

Jaffee, S. R., Moffitt, T. E., Caspi, A., Fombonne, E., Poulton, R., & Martin, J. (2002). Differences in early childhood risk factors for juvenile-onset and adult-onset depression. *Archives of General Psychiatry, 59*(3), 215-222.

Jain, S., Shapiro, S. L., Swanick, S., Roesch, S. C., Mills, P. J., & Schwartz, G. E. (2007). A randomized controlled trial of mindfulness meditation versus relaxation training: Effects on distress, positive states of mind, rumination, and distraction. *Annals of Behavioral Medicine, 33*(1), 11-21.

Johnson, D. P., Whisman, M. A., Corley, R. P., Hewitt, J. K., & Friedman, N. P. (2014). Genetic and environmental influences on rumination and its covariation with depression. *Cognition and Emotion, 28*(7), 1270-1286.

Johnson, W., Krueger, R. F., Bouchard, T. J., & McGue, M. (2002). The personalities of twins: Just ordinary folks. *Twin Research, 5*(02), 125-131.

Joiner, T. E., Catanzaro, S. J., & Laurent, J. (1996). Tripartite structure of postive and negative affect, depression, and anxiety in child and adolescent psychiatric inpatients. *Journal of Abnormal Psychology, 105*(3), 401-409.

Joiner, T. E., Schmidt, N. B., Schmidt, K. L., Laurent, J., Catanzaro, S. J., Perez, M., & Pettit, J. W. (2002). Anxiety sensitivity as a specific and unique marker of anxious symptoms in youth psychiatric inpatients. *Journal of Abnormal Child Psychology, 30*(2), 167-175.

Joormann, J., & Gotlib, I. H. (2010). Emotion regulation in depression: relation to cognitive inhibition. *Cognition and Emotion, 24*(2), 281-298.

Joormann, J., Talbot, L., & Gotlib, I. H. (2007). Biased processing of emotional information in girls at risk for depression. *Journal of Abnormal Psychology, 116*(1), 135.

Kaliman, P., Álvarez-López, M. J., Cosín-Tomás, M., Rosenkranz, M. A., Lutz, A., & Davidson, R. J. (2014). Rapid changes in histone deacetylases and inflammatory gene expression in expert meditators. *Psychoneuroendocrinology, 40*, 96-107.

Katon, W., Richardson, L., Russo, J., McCarty, C. A., Rockhill, C., McCauley, E., . . . Grossman, D. C. (2010). Depressive symptoms in adolescence: the association with multiple health risk behaviors. *General Hospital Psychiatry, 32*(3), 233-239.

Kearney, C. A., Albano, A., Eisen, A. R., Allan, W. D., & Barlow, D. H. (1997). The phenomenology of panic disorder in youngsters: An empirical study of a clinical sample. *Journal of Anxiety Disorders, 11*(1), 49-62.

Keers, R., & Aitchison, K. J. (2011). Pharmacogenetics of antidepressant response. *Expert Review of Neurotherapeutics, 11*(1), 101-125. doi:10.1586/ern.10.186

Kendler, K. S. (1996). Major depression and generalised anxiety disorder. Same genes, (partly)different environments--revisited. *British Journal of Psychiatry Supplement*(30), 68-75.

Kendler, K. S., Aggen, S. H., Knudsen, G. P., Røysamb, E., Neale, M. C., & Reichborn-Kjennerud, T. (2011). The structure of genetic and environmental risk factors for syndromal and subsyndromal common DSM-IV axis I and all axis II disorders. *The American journal of psychiatry, 168*(1), 29-39.

Kendler, K. S., & Baker, J. H. (2007). Genetic influences on measures of the environment: a systematic review. *Psychological Medicine, 37*(5), 615-626.

Kendler, K. S., Bulik, C. M., Silberg, J., Hettema, J. M., Myers, J., & Prescott, C. A. (2000). Childhood sexual abuse and adult psychiatric and substance use disorders in women: an epidemiological and cotwin control analysis. *Archives of General Psychiatry, 57*(10), 953-959.

Kendler, K. S., Davis, C. G., & Kessler, R. C. (1997). The familial aggregation of common psychiatric and substance use disorders in the National Comorbidity Survey: a family history study. *The British Journal of Psychiatry, 170*(6), 541-548.

Kendler, K. S., Eaves, L. J., Loken, E. K., Pedersen, N. L., Middeldorp, C. M., Reynolds, C., . . . Gardner, C. O. (2011). The impact of environmental experiences on symptoms of anxiety and depression across the life span. *Psychological Science, 22*(10), 1343-1352.

Kendler, K. S., Gardner, C. O., Annas, P., Neale, M. C., Eaves, L. J., & Lichtenstein, P. (2008). A longitudinal twin study of fears from middle childhood to early adulthood: evidence for a developmentally dynamic genome. *Archives of General Psychiatry, 65*(4), 421-429.

Kendler, K. S., Gardner, C. O., Gatz, M., & Pedersen, N. L. (2007). The sources of co-morbidity between major depression and generalized anxiety disorder in a Swedish national twin sample. *Psychological Medicine, 37*(03), 453-462.

Kendler, K. S., Gardner, C. O., & Lichtenstein, P. (2008). A developmental twin study of symptoms of anxiety and depression: evidence for genetic innovation and attenuation. *Psychological Medicine, 38*(11), 1567-1575.

Kendler, K. S., Heath, A. C., Martin, N. G., & Eaves, L. J. (1987). Symptoms of anxiety and symptoms of depression. Same genes, different environments? *Archives of General Psychiatry, 44*(5), 451-457.

Kendler, K. S., Hettema, J. M., Butera, F., Gardner, C. O., & Prescott, C. A. (2003). Life event dimensions of loss, humiliation, entrapment, and danger in the prediction of onsets of major depression and generalized anxiety. *Archives of General Psychiatry, 60*(8), 789-796.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1992a). Generalized anxiety disorder in women. A population-based twin study. *Archives of General Psychiatry, 49*(4), 267-272.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1992b). Major depression and generalized anxiety disorder. Same genes, (partly) different environments? *Archives of General Psychiatry, 49*(9), 716-722.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1992c). A population-based twin study of major depression in women. The impact of varying definitions of illness. *Archives of General Psychiatry, 49*(4), 257-266.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1993a). Major depression and phobias: the genetic and environmental sources of comorbidity. *Psychological Medicine, 23*, 361-371.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1993b). A test of the equal-environment assumption in twin studies of psychiatric illness. *Behavior Genetics, 23*(1), 21-27.

Kendler, K. S., Prescott, C. A., Myers, J., & Neale, M. C. (2003). The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Archives of General Psychiatry, 60*(9), 929-937.

Kendler, K. S., Walters, E. E., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1995). The structure of the genetic and environmental risk factors for six major psychiatric disorders in women: Phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. *Archives of General Psychiatry, 52*, 374-383.

Keng, S.-L., Smoski, M. J., & Robins, C. J. (2011). Effects of mindfulness on psychological health: A review of empirical studies. *Clinical psychology review, 31*(6), 1041-1056.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., . . . Wang, P. S. (2003). The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *Jama, 289*(23), 3095-3105.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*(6), 593-602.

Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*(6), 617-627.

Kessler, R. C., & Frank, R. G. (1997). The impact of psychiatric disorders on work loss days. *Psychological Medicine, 27*(04), 861-873.

Kessler, R. C., Stang, P. E., Wittchen, H. U., Ustun, T. B., Roy-Byrne, P. P., & Walters, E. E. (1998). Lifetime panic-depression comorbidity in the National Comorbidity Survey. *Archives of General Psychiatry, 55* 801-808.

Keyes, K., Eaton, N., Krueger, R., Skodol, A., Wall, M., Grant, B., . . . Hasin, D. (2013). Thought disorder in the meta-structure of psychopathology. *Psychological Medicine, 43*(08), 1673-1683.

Klauke, B., Deckert, J., Reif, A., Pauli, P., Zwanzger, P., Baumann, C., . . . Domschke, K. (2011). Serotonin transporter gene and childhood trauma — a G × E effect on anxiety sensitivity. *Depression and anxiety, 28*(12), 1048-1057. doi:10.1002/da.20840

Klein, D., Lewinsohn, P., Rohde, P., Seeley, J., & Shankman, S. (2003). Family study of co-morbidity between major depressive disorder and anxiety disorders. *Psychological Medicine, 33*(04), 703-714.

Klenberg, L., Korkman, M., & Lahti-Nuuttila, P. (2001). Differential development of attention and executive functions in 3-to 12-year-old Finnish children. *Developmental Neuropsychology, 20*(1), 407-428.

Kley, H., Heinrichs, N., Bender, C., & Tuschen-Caffier, B. (2012). Predictors of outcome in a cognitive-behavioral group program for children and adolescents with social anxiety disorder. *Journal of Anxiety Disorders, 26*(1), 79-87.

Koenen, K. C., Lyons, M. J., Goldberg, J., Simpson, J., Williams, W. M., Toomey, R., . . . Wolfe, J. (2003). A high risk twin study of combat-related PTSD comorbidity. *Twin Research, 6*(3), 218-226.

Korczak, D. J., & Goldstein, B. I. (2009). Childhood onset major depressive disorder: course of illness and psychiatric comorbidity in a community sample. *The Journal of pediatrics, 155*(1), 118-123.

Koster, E. H., De Lissnyder, E., Derakshan, N., & De Raedt, R. (2011). Understanding depressive rumination from a cognitive science perspective: The impaired disengagement hypothesis. *Clinical psychology review, 31*(1), 138-145.

Kotov, R., Bromet, E. J., Schechter, C., Broihier, J., Feder, A., Friedman-Jimenez, G., . . . Moline, J. (2015). Posttraumatic stress disorder and the risk of respiratory problems in World Trade Center responders: longitudinal test of a pathway. *Psychosomatic Medicine, 77*(4), 438-448.

Kotov, R., Perlman, G., Gámez, W., & Watson, D. (2014). The structure and short-term stability of the emotional disorders: a dimensional approach. *Psychological Medicine*, 1-12.

Kovacs, M. (1985). The Children's Depression Inventory (CDI). *Psychopharmacology Bulletin, 21*, 995-1124.

Krueger, R. F. (1999). The structure of common mental disorders. *Archives of General Psychiatry, 56*(10), 921-926.

Krueger, R. F., Caspi, A., Moffitt, T. E., & Silva, P. A. (1998). The structure and stability of common mental disorders (DSM-III-R): A longitudinal-epidemiological study. *Journal of Abnormal Psychology, 107*, 216-227.

Krueger, R. F., & Eaton, N. R. (2015). Transdiagnostic factors of mental disorders. *World Psychiatry, 14*(1), 27-29.

Krueger, R. F., & Finger, M. S. (2001). Using item response theory to understand comorbidity among anxiety and unipolar mood disorders. *Psychological Assessment, 13*(1), 140-151.

Krueger, R. F., Moffitt, T. E., Caspi, A., Bleske, A., & Silva, P. A. (1998). Assortative mating for antisocial behavior: Developmental and methodological implications. *Behavior Genetics, 28*(3), 173-186.

Kushner, M., Krueger, R., Wall, M., Maurer, E., Menk, J., & Menary, K. (2013). Modeling and treating internalizing psychopathology in a clinical trial: a latent variable structural equation modeling approach. *Psychological Medicine, 43*(08), 1611-1623.

Kuyken, W., Hayes, R., Barrett, B., Byng, R., Dalgleish, T., Kessler, D., . . . Cardy, J. (2015). Effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse or recurrence (PREVENT): a randomised controlled trial. *The Lancet*.

Kuyken, W., Watkins, E., Holden, E., White, K., Taylor, R. S., Byford, S., . . . Dalgleish, T. (2010). How does mindfulness-based cognitive therapy work? *Behaviour Research and Therapy, 48*(11), 1105-1112.

Kyte, Z. A., Goodyer, I. M., & Sahakian, B. J. (2005). Selected executive skills in adolescents with recent first episode major depression. *Journal of child psychology and psychiatry, 46*(9), 995-1005.

Lahey, B. B., Applegate, B., Waldman, I. D., Loft, J. D., Hankin, B. L., & Rick, J. (2004). The structure of child and adolescent psychopathology: generating new hypotheses. *Journal of Abnormal Psychology, 113*(3), 358-385.

Lahey, B. B., Rathouz, P. J., Van Hulle, C., Urbano, R. C., Krueger, R. F., Applegate, B., . . . Waldman, I. D. (2008). Testing structural models of DSM-IV symptoms of common forms of child and adolescent psychopathology. *Journal of Abnormal Child Psychology, 36*(2), 187-206.

Lahey, B. B., Van Hulle, C. A., Singh, A. L., Waldman, I. D., & Rathouz, P. J. (2011). Higher-order genetic and environmental structure of prevalent forms of child and adolescent psychopathology. *Archives of General Psychiatry, 68*(2), 181-189.

Lahey, B. B., Zald, D. H., Hakes, J. K., Krueger, R. F., & Rathouz, P. J. (2014). Patterns of heterotypic continuity associated with the cross-sectional correlational structure of prevalent mental disorders in adults. *JAMA Psychiatry, 71*(9), 989-996.

Lane, H.-Y., Liu, Y.-C., Huang, C.-L., Hsieh, C.-L., Chang, Y.-L., Chang, L., . . . Chang, W.-H. (2008). Prefrontal executive function and D1, D3, 5-HT2A and 5-HT6 receptor gene variations in healthy adults. *Journal of psychiatry & neuroscience: JPN, 33*(1), 47.

Langley, A. K., Bergman, R. L., McCracken, J., & Piacentini, J. C. (2004). Impairment in childhood anxiety disorders: preliminary examination of the child anxiety impact scale-parent version. *Journal of child and adolescent psychopharmacology, 14*(1), 105-114. Retrieved from http://ukpmc.ac.uk/abstract/MED/15142397

Lau, J., Hilbert, K., Goodman, R., Gregory, A. M., Pine, D. S., Viding, E. M., & Eley, T. C. (2012). Investigating the genetic and environmental bases of biases in threat recognition and avoidance in children with anxiety problems. *Biol. Mood. Anxiety Disord, 2*, 12.

Lau, J. Y., Belli, S. R., Gregory, A. M., & Eley, T. C. (2014). Interpersonal cognitive biases as genetic markers for pediatric depressive symptoms: Twin data from the Emotions, Cognitions, Heredity and Outcome (ECHO) study. *Development and Psychopathology, 26*(4pt2), 1267-1276.

Lau, J. Y., Burt, M., Leibenluft, E., Pine, D. S., Rijsdijk, F., Shiffrin, N., & Eley, T. C. (2009). Individual differences in children's facial expression recognition ability: The role of nature and nurture. *Developmental Neuropsychology, 34*(1), 37-51.

Lau, J. Y. F., & Eley, T. C. (2006). Changes in genetic and environmental influences on depressive symptoms across adolescence and young adulthood. *British Journal of Psychiatry, 189*(5), 422-427.

Lau, J. Y. F., & Eley, T. C. (2008a). Attributional style as a risk marker of genetic effects for adolescent depressive symptoms. *Journal of Abnormal Psychology, 117*(4), 849-859.

Lau, J. Y. F., & Eley, T. C. (2008b). Disentangling gene environment correlations and interactions in adolescent depression. *Journal of child psychology and psychiatry, 49*(2), 142-150.

Lau, J. Y. F., Gregory, A. M., Goldwin, M. A., Pine, D. S., & Eley, T. C. (2007). Assessing gene-environment interactions on anxiety symptom subtypes across childhood and adolescence. *Development and Psychopathology, 19*, 1129-1146.

Lau, J. Y. F., Rijsdijk, F. V., & Eley, T. C. (2006). I think, therefore I am: A twin study of attributional style in adolescents. *Journal of child psychology and psychiatry, 47*(7), 696-703.

Leckman, J. F., Merikangas, K. R., Pauls, D. L., Prusoff, B. A., & Weissman, M. M. (1983). Anxiety disorders and depression: contradictions between family study data and DSM-III conventions. *American Journal of Psychiatry, 140*(7), 880-882.

Lee, A., & Hankin, B. L. (2009). Insecure attachment, dysfunctional attitudes, and low self-esteem predicting prospective symptoms of depression and anxiety during adolescence. *Journal of Clinical Child & Adolescent Psychology, 38*(2), 219-231.

Lerner, D., Adler, D. A., Chang, H., Lapitsky, L., Hood, M. Y., Perissinotto, C., . . . Rogers, W. H. (2004). Unemployment, job retention, and productivity loss among employees with depression. *Psychiatric Services, 55*(12), 1371-1378.

Lester, K. J., & Eley, T. C. (2013). Therapygenetics: Using genetic markers to predict response to psychological treatment for mood and anxiety disorders. *Biology of mood & anxiety disorders, 3*(4), 1-16. doi:10.1186/2045-5380-3-4

Lester, K. J., Field, A. P., & Muris, P. (2011). Experimental modification of interpretation bias regarding social and animal fear in children. *Journal of Anxiety Disorders, 25*(5), 697-705. doi:http://dx.doi.org/10.1016/j.janxdis.2011.03.006

Lester, K. J., Seal, K., Nightingale, Z. C., & Field, A. P. (2010). Are children's own interpretations of ambiguous situations based on how they perceive their mothers have interpreted ambiguous situations for them in the past? *Journal of Anxiety Disorders, 24*(1), 102-108.

Lewinsohn, P. M., Gotlib, I. H., Lewinsohn, M., Seeley, J. R., & Allen, N. B. (1998). Gender differences in anxiety disorders and anxiety symptoms in adolescents. *Journal of Abnormal Psychology, 107*, 109-117.

Lewinsohn, P. M., Rohde, P., & Seeley, J. R. (1995). Adolescent psychopathology: III. The clinical consequences of comorbidity. *Journal of the American Academy of Child and Adolescent Psychiatry, 34*(4), 510-519.

Lewis, G. J., & Plomin, R. (2015). Heritable influences on behavioural problems from early childhood to mid-adolescence: evidence for genetic stability and innovation. *Psychological Medicine, FirstView Article*.

Li, W., & Zinbarg, R. E. (2007). Anxiety Sensitivity and Panic Attacks A 1-Year Longitudinal Study. *Behavior Modification, 31*(2), 145-161.

Lipp, O. V., & Waters, A. M. (2007). When danger lurks in the background: Attentional capture by animal fear-relevant distractors is specific and selectively enhanced by animal fear. *Emotion, 7*(1), 192.

Litcher-Kelly, L., Lam, Y., Broihier, J. A., Brand, D. L., Banker, S. V., Kotov, R., . . . Luft, B. J. (2014). Longitudinal Study of the Impact of Psychological Distress Symptoms on New-Onset Upper Gastrointestinal Symptoms in World Trade Center Responders. *Psychosomatic Medicine, 76*(9), 686-693.

Lonigan, C. J., & Vasey, M. W. (2009). Negative affectivity, effortful control, and attention to threat-relevant stimuli. *Journal of Abnormal Child Psychology, 37*(3), 387-399.

Lothmann, C., Holmes, E. A., Chan, S. W. Y., & Lau, J. Y. F. (2011). Cognitive bias modification training in adolescents: effects on interpretation biases and mood. *Journal of child psychology and psychiatry, 52*(1), 24-32. doi:10.1111/j.1469-7610.2010.02286.x

Lubke, G. H., Hottenga, J. J., Walters, R., Laurin, C., De Geus, E. J., Willemsen, G., . . . Vink, J. M. (2012). Estimating the genetic variance of major depressive disorder due to all single nucleotide polymorphisms. *Biological Psychiatry, 72*(8), 707-709.

Ludwig, D. S., & Kabat-Zinn, J. (2008). Mindfulness in medicine. *Jama, 300*(11), 1350-1352.

Lyche, P., Jonassen, R., Stiles, T., Ulleberg, P., & Landrø, N. (2011). Attentional functions in major depressive disorders with and without comorbid anxiety. *Archives of clinical neuropsychology, 26*(1), 38-47.

Lyche, P., Jonassen, R., Stiles, T. C., Ulleberg, P., & Landrø, N. I. (2010). Cognitive control functions in unipolar major depression with and without co-morbid anxiety disorder. *Frontiers in psychiatry, 1*.

MacLeod, C., Mathews, A., & Tata, P. (1986). Attentional bias in emotional disorders. *Journal of Abnormal Psychology, 95*(1), 15-20.

MacLeod, C., Rutherford, E., Campbell, L., Ebsworthy, G., & Holker, L. (2002). Selective attention and emotional vulnerability: assessing the causal basis of their association through the experimental manipulation of attentional bias. *Journal of Abnormal Psychology, 111*(1), 107.

MacLeod, C. M. (1991). Half a century of research on the Stroop effect: an integrative review. *Psychological Bulletin, 109*(2), 163.

MacQueen, G., & Frodl, T. (2011). The hippocampus in major depression: evidence for the convergence of the bench and bedside in psychiatric research&quest. *Molecular Psychiatry, 16*(3), 252-264.

Maes, H. H., Neale, M. C., Kendler, K. S., Hewitt, J. K., Silberg, J. L., Foley, D. L., . . . Eaves, L. J. (1998). Assortative mating for major psychiatric diagnoses in two population-based samples. *Psychological Medicine, 28*(6), 1389-1401.

Maier, W., Minges, J., & Lichtermann, D. (1995). The familial relationship between panic disorder and unipolar depression. *Journal of Psychiatric Research, 29*(5), 375-388.

Maller, R. G., & Reiss, S. (1992). Anxiety sensitivity in 1984 and panic attacks in 1987. *Journal of Anxiety Disorders, 6*(3), 241-247.

Manicavasgar, V., Parker, G., & Perich, T. (2011). Mindfulness-based cognitive therapy vs cognitive behaviour therapy as a treatment for non-melancholic depression. *Journal of Affective Disorders, 130*(1), 138-144.

Mannuzza, S., Chapman, T. F., Klein, D. F., & Fyer, A. J. (1994). Familial transmission of panic disorder: effect of major depression comorbidity. *Anxiety, 1*(4), 180-185.

March, J., Silva, S., Petrycki, S., Curry, J., Wells, K., Fairbank, J., . . . Vitiello, B. (2004). Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA: the journal of the American Medical Association, 292*(7), 807-820.

Marks, I. f., & Nesse, R. M. (1994). Fear and fitness: An evolutionary analysis of anxiety disorders. *Ethology and Sociobiology, 15*(5â€“6), 247-261. Retrieved from http://www.sciencedirect.com/science/article/pii/0162309594900027

Mathews, A., & MacLeod, C. (2002). Induced processing biases have causal effects on anxiety. *Cognition and Emotion, 16*(3), 331-354.

Mathews, A., & MacLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annu. Rev. Clin. Psychol., 1*, 167-195.

Mathews, C. A., & Reus, V. I. (2001). Assortative mating in the affective disorders: a systematic review and meta-analysis. *Comprehensive Psychiatry, 42*(4), 257-262.

McAdams, T. A., Gregory, A. M., Rowe, R., Zavos, H., Barclay, N. L., Lau, J. Y., . . . Eley, T. C. (2013). The genesis 12–19 (G1219) study: a twin and sibling study of gene–environment interplay and adolescent development in the UK. *Twin Research & Human Genetics, 1*(1), 1-10.

McCracken, L. M., & Keogh, E. (2009). Acceptance, mindfulness, and values-based action may counteract fear and avoidance of emotions in chronic pain: an analysis of anxiety sensitivity. *The Journal of Pain, 10*(4), 408-415.

McCrone, P., Dhanasiri, S., Patel, A., Knapp, M., & Lawton-Smith, S. (2008). *Paying the price. The cost of mental health care in England to 2026*. Retrieved from

McEvoy, P. M., & Mahoney, A. E. (2012). To be sure, to be sure: Intolerance of uncertainty mediates symptoms of various anxiety disorders and depression. *Behavior Therapy, 43*(3), 533-545.

McEvoy, P. M., Nathan, P., & Norton, P. J. (2009). Efficacy of transdiagnostic treatments: A review of published outcome studies and future research directions. *Journal of Cognitive Psychotherapy, 23*(1), 20-33.

McEvoy, P. M., Watson, H., Watkins, E. R., & Nathan, P. (2013). The relationship between worry, rumination, and comorbidity: Evidence for repetitive negative thinking as a transdiagnostic construct. *Journal of Affective Disorders, 151*(1), 313-320.

McGlinchey, J. B., & Zimmerman, M. (2007). Examining a dimensional representation of depression and anxiety disorders' comorbidity in psychiatric outpatients with item response modeling. *Journal of Abnormal Psychology, 116*(3), 464.

McKinnon, M. C., Yucel, K., Nazarov, A., & MacQueen, G. M. (2009). A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. *Journal of psychiatry & neuroscience: JPN, 34*(1), 41.

McLaughlin, K. A., & Hatzenbuehler, M. L. (2009). Stressful life events, anxiety sensitivity, and internalizing symptoms in adolescents. *Journal of Abnormal Psychology, 118*(3), 659.

McLaughlin, K. A., Mennin, D. S., & Farach, F. J. (2007). The contributory role of worry in emotion generation and dysregulation in generalized anxiety disorder. *Behaviour Research and Therapy, 45*(8), 1735-1752.

McLaughlin, K. A., & Nolen-Hoeksema, S. (2011). Rumination as a transdiagnostic factor in depression and anxiety. *Behaviour Research and Therapy, 49*(3), 186-193.

McNally, R. J. (1995). Automaticity and the anxiety disorders. *Behaviour Research and Therapy, 33*(7), 747-754.

McWilliams, L. A., Becker, E. S., Margraf, J., Clara, I. P., & Vriends, N. (2007). Anxiety disorder specificity of anxiety sensitivity in a community sample of young women. *Personality and Individual Differences, 42*(2), 345-354.

Meiran, N., Diamond, G. M., Toder, D., & Nemets, B. (2011). Cognitive rigidity in unipolar depression and obsessive compulsive disorder: Examination of task switching, Stroop, working memory updating and post-conflict adaptation. *Psychiatry Research, 185*(1), 149-156.

Meltzer, H., Gatward, R., Goodman, R., & Ford, T. (2000). *Mental health of children and adolescents in Great Britain*. London: The Stationary Office.

Mendlewicz, J., Papadimitriou, G., & Wilmotte, J. (1993). Family study of panic disorder: Comparison with generalized anxiety disorder, major depression, and normal subjects. *Psychiatric Genetics, 3*, 73-78.

Mennin, D. S., Heimberg, R. G., Fresco, D. M., & Ritter, M. R. (2008). Is generalized anxiety disorder an anxiety or mood disorder? Considering multiple factors as we ponder the fate of GAD. *Depression and anxiety, 25*(4), 289-299.

Merikangas, K. R., & Angst, J. (1995). Comorbidity and social phobia: evidence from clinical, epidemiologic, and genetic studies. *European Archives of Psychiatry and Clinical Neuroscience, 244*(6), 297-303.

Merrell, K. W., McClun, L. A., Kempf, K. K. G., & Lund, J. (2002). Using self-report assessment to identify children with internalizing problems: Validity of the internalizing symptoms scale for children. *Journal of Psychoeducational Assessment, 20*, 223-239.

Michael, K. D., & Merrell, K. W. (1998). Reliability of children's self-reported internalizing symptoms over short to medium-length time intervals. *Journal of the American Academy of Child and Adolescent Psychiatry, 37*(2), 194-201.

Mineka, S., Watson, D., & Clark, L. A. (1998). Comorbidity of Anxiety and Unipolar Mood Disorders. *Annual Review of Psychology, 49*, 377-412.

Miranda, R., & Mennin, D. S. (2007). Depression, generalized anxiety disorder, and certainty in pessimistic predictions about the future. *Cognitive Therapy and Research, 31*(1), 71-82.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cognitive Psychology, 41*(1), 49-100.

Moffitt, T. E., Harrington, H., Caspi, A., Kim-Cohen, J., Goldberg, D., Gregory, A. M., & Poulton, R. (2007). Depression and generalized anxiety disorder: cumulative and sequential comorbidity in a birth cohort followed prospectively to age 32 years. *Archives of General Psychiatry, 64*(6), 651-660.

Mogg, K., Bradbury, K. E., & Bradley, B. P. (2006). Interpretation of ambiguous information in clinical depression. *Behaviour Research and Therapy, 44*(10), 1411-1419.

Mogg, K., & Bradley, B. P. (2005). Attentional bias in generalized anxiety disorder versus depressive disorder. *Cognitive Therapy and Research, 29*(1), 29-45.

Mogg, K., Millar, N., & Bradley, B. P. (2000). Biases in eye movements to threatening facial expressions in generalized anxiety disorder and depressive disorder. *Journal of Abnormal Psychology, 109*(4), 695-704.

Mogg, K., Salum, G., Bradley, B., Gadelha, A., Pan, P., Alvarenga, P., . . . Manfro, G. (2015). Attention network functioning in children with anxiety disorders, attention-deficit/hyperactivity disorder and non-clinical anxiety. *Psychological Medicine*, 1-14.

Mogg, K., Wilson, K. A., Hayward, C., Cunning, D., & Bradley, B. P. (2012). Attentional biases for threat in at-risk daughters and mothers with lifetime panic disorder. *Journal of Abnormal Psychology, 121*(4), 852.

Mohlman, J., & Gorman, J. M. (2005). The role of executive functioning in CBT: a pilot study with anxious older adults. *Behaviour Research and Therapy, 43*(4), 447-465.

Moilanen, I., Linna, S. L., Ebeling, H., Kumpulainen, K., Tamminen, T., Piha, J., & Almqvist, F. (1999). Are twins' behavioural/emotional problems different from singletons'? *European Child & Adolescent Psychiatry.8 Suppl 4:62-7*.

Monga, S., Birmaher, B., Chiappetta, L., Brent, D., Kaufman, J., Bridge, J., & Cully, M. (2000). Screen for Child Anxiety-Related Emotional Disorders (SCARED): convergent and divergent validity. *Depression and Anxiety, 12*(2), 85-91.

Moore, M. N., Salk, R. H., Van Hulle, C. A., Abramson, L. Y., Hyde, J. S., Lemery-Chalfant, K., & Goldsmith, H. H. (2013). Genetic and environmental influences on rumination, distraction, and depressed mood in adolescence. *Clinical Psychological Science, 1*(3), 316-322.

Moradi, A. R., Taghavi, R., Neshat-Doost, H. T., Yule, W., & Dalgleish, T. (2000). Memory bias for emotional information in children and adolescents with posttraumatic stress disorder: A preliminary study. *Journal of Anxiety Disorders, 14*(5), 521-534.

Moran, T. P., & Moser, J. S. (2014). The color of anxiety: Neurobehavioral evidence for distraction by perceptually salient stimuli in anxiety. *Cognitive, Affective, & Behavioral Neuroscience*, 1-11.

Moser, J. S., Becker, M. W., & Moran, T. P. (2012). Enhanced attentional capture in trait anxiety. *Emotion, 12*(2), 213-216.

Mosing, M. A., Gordon, S. D., Medland, S. E., Statham, D. J., Nelson, E. C., Heath, A. C., . . . Wray, N. R. (2009). Genetic and environmental influences on the co-morbidity between depression, panic disorder, agoraphobia, and social phobia: a twin study. *Depression and anxiety, 26*(11), 1004-1011.

Mrazek, M. D., Franklin, M. S., Phillips, D. T., Baird, B., & Schooler, J. W. (2013). Mindfulness training improves working memory capacity and GRE performance while reducing mind wandering. *Psychological Science*, 0956797612459659.

Mrazek, M. D., Smallwood, J., & Schooler, J. W. (2012). Mindfulness and mind-wandering: finding convergence through opposing constructs. *Emotion, 12*(3), 442-448.

Muris, P. (2002). An expanded childhood anxiety sensitivity index: its factor structure, reliability, and validity in a non-clinical adolescent sample. *Behaviour Research and Therapy, 40*(3), 299-311.

Muris, P., & Field, A. P. (2008). Distorted cognition and pathological anxiety in children and adolescents. *Cognition & emotion, 22*(3), 395-421.

Muris, P., Hoeve, I., Meesters, C., & Mayer, B. (2004). Children's perception and interpretation of anxiety-related physical symptoms. *Journal of Behavior Therapy and Experimental Psychiatry, 35*(3), 233-244. doi:10.1016/j.jbtep.2004.03.008

Muris, P., Meesters, C., & Rompelberg, L. (2007). Attention control in middle childhood: Relations to psychopathological symptoms and threat perception distortions. *Behaviour Research and Therapy, 45*(5), 997-1010.

Muris, P., Merckelbach, H., Ollendick, T., King, N., & Bogie, N. (2002). Three traditional and three new childhood anxiety questionnaires: Their reliability and validity in a normal adolescent sample. *Behaviour Research and Therapy, 40*(7), 753-772.

Muris, P., Roelofs, J., Rassin, E., Franken, I., & Mayer, B. (2005). Mediating effects of rumination and worry on the links between neuroticism, anxiety and depression. *Personality and Individual Differences, 39*(6), 1105-1111.

Muris, P., van der Pennen, E., Sigmond, R., & Mayer, B. (2008). Symptoms of anxiety, depression, and aggression in non-clinical children: Relationships with self-report and performance-based measures of attention and effortful control. *Child Psychiatry and Human Development, 39*(4), 455-467.

Naragon-Gainey, K. (2010). Meta-analysis of the relations of anxiety sensitivity to the depressive and anxiety disorders. *Psychological Bulletin, 136*(1), 128-150.

National Collaborating Centre for Mental Health. (2010). *Depression: the treatment and management of depression in adults (updated edition)*.

Neale, M. C., & Cardon, L. R. (1992). *Methodology for genetic studies of twins and families*. Dordrecht: Kluwer Academic Publications.

Nelson, E. C., Grant, J. D., Bucholz, K. K., Glowinski, A., Madden, P. A. F., Reich, W., & Heath, A. C. (2000). Social phobia in a population-based female adolescent twin sample: co-morbidity and associated suicide-related symptoms. *Psychological Medicine, 30*(4), 797-804.

Neshat-Doost, H. T., Moradi, A. R., Taghavi, M. R., Yule, W., & Dalgleish, T. (2000). Lack of attentional bias for emotional information in clinically depressed children and adolescents on the dot probe task. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 41*(3), 363-368.

Nivard, M., Dolan, C., Kendler, K., Kan, K., Willemsen, G., van Beijsterveldt, C., . . . Bartels, M. (2014). Stability in symptoms of anxiety and depression as a function of genotype and environment: a longitudinal twin study from ages 3 to 63 years. *Psychological Medicine*, 1-11.

Noël, V., & Francis, S. (2011). A Meta-analytic Review of the Role of Child Anxiety Sensitivity in Child Anxiety. *Journal of Abnormal Child Psychology, 39*(5), 721-733. doi:10.1007/s10802-011-9489-3

Noel, V. A., Lewis, K., Francis, S. E., & Mezo, P. G. (2013). Relationships between the multiple dimensions of anxiety sensitivity and symptoms of anxiety and depression in men and women. *Journal of Cognitive and Behavioral Psychotherapies*(13), 333-353.

Nolen-Hoeksema, S. (2000). The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. *Journal of Abnormal Psychology, 109*(3), 504.

Nolen-Hoeksema, S., & Watkins, E. R. (2011). A heuristic for developing transdiagnostic models of psychopathology explaining multifinality and divergent trajectories. *Perspectives on Psychological Science, 6*(6), 589-609.

O'Connor, T. G., McGuire, S., Reiss, D., Hetherington, E. M., & Plomin, R. (1998). Co-occurrence of depressive symptoms and antisocial behavior in adolescence: A common genetic liability. *Journal of Abnormal Psychology, 107*, 27-37.

O'Connor, T. G., Neiderhiser, J. M., Reiss, D., Hetherington, E. M., & Plomin, R. (1998). Genetic contributions to continuity, change, and co-occurrence of antisocial and depressive symptoms in Adolescence. *Journal of child psychology and psychiatry, 39*, 323-336.

O'Neil, K. A., Podell, J. L., Benjamin, C. L., & Kendall, P. C. (2010). Comorbid depressive disorders in anxiety-disordered youth: Demographic, clinical, and family characteristics. *Child Psychiatry and Human Development, 41*(3), 330-341.

Ogliari, A., Citterio, A., Zanoni, A., Fagnani, C., Patriarca, V., Cirrincione, R., . . . Battaglia, M. (2006). Genetic and environmental influences on anxiety dimensions in Italian twins evaluated with the SCARED questionnaire. *Journal of Anxiety Disorders, 20*(6), 760-777.

Ogliari, A., Spatola, C. A., Pesenti-Gritti, P., Medda, E., Penna, L., Stazi, M. A., . . . Fagnani, C. (2010). The role of genes and environment in shaping co-occurrence of DSM-IV defined anxiety dimensions among Italian twins aged 8-17. *Journal of Anxiety*

Disorders, 24(4), 433-439. Retrieved from http://www.sciencedirect.com/science/article/pii/S0887618510000356

Öhman, A., Flykt, A., & Esteves, F. (2001). Emotion drives attention: detecting the snake in the grass. *Journal of Experimental Psychology: General, 130*(3), 466.

Olatunji, B. O., Naragon-Gainey, K., & Wolitzky-Taylor, K. B. (2013). Specificity of rumination in anxiety and depression: a multimodal meta-analysis. *Clinical psychology: Science and practice, 20*(3), 225-257.

Olatunji, B. O., & Wolitzky-Taylor, K. B. (2009). Anxiety Sensitivity and the Anxiety Disorders: A Meta-Analytic Review and Synthesis. *Psychological Bulletin, 135*(6), 974-999.

Olino, T. M., Klein, D. N., Lewinsohn, P. M., Rohde, P., & Seeley, J. R. (2008). Longitudinal associations between depressive and anxiety disorders: a comparison of two trait models. *Psychological Medicine, 38*(03), 353-363.

Ollendick, T. H., Öst, L.-G., Reuterskiöld, L., & Costa, N. (2010). Comorbidity in youth with specific phobias: Impact of comorbidity on treatment outcome and the impact of treatment on comorbid disorders. *Behaviour Research and Therapy, 48*(9), 827-831.

Owens, M., Stevenson, J., Hadwin, J. A., & Norgate, R. (2012). Anxiety and depression in academic performance: An exploration of the mediating factors of worry and working memory. *School Psychology International, 33*(4), 433-449.

Papay, J. P., & Hedl Jr, J. J. (1978). Psychometric characteristics and norms for disadvantaged third and fourth grade children on the State-Trait Anxiety Inventory for Children. *Journal of Abnormal Child Psychology, 6*(1), 115-120.

Parsons, T. D., & Rizzo, A. A. (2008). Affective outcomes of virtual reality exposure therapy for anxiety and specific phobias: A meta-analysis. *Journal of Behavior Therapy and Experimental Psychiatry, 39*(3), 250-261.

Peckham, A. D., McHugh, R. K., & Otto, M. W. (2010). A meta-analysis of the magnitude of biased attention in depression. *Depression and anxiety, 27*(12), 1135-1142.

Peers, P. V., & Lawrence, A. D. (2009). Attentional control of emotional distraction in rapid serial visual presentation. *Emotion, 9*(1), 140-145.

Pergamin-Hight, L., Bakermans-Kranenburg, M. J., van IJzendoorn, M. H., & Bar-Haim, Y. (2012). Variations in the promoter region of the serotonin transporter gene and biased attention for emotional information: a meta-analysis. *Biological Psychiatry, 71*(4), 373-379.

Pessoa, L., & Ungerleider, L. G. (2004). Neuroimaging studies of attention and the processing of emotion-laden stimuli. *Progress in Brain Research, 144*, 171-182.

Peterson, R. A., & Plehn, K. (1999). Measuring anxiety sensitivity. In S. Taylor (Ed.), *Anxiety Sensitivity: Theory, Research, and Treatment of the Fear of Anxiety* (pp. 61-81). Mahwah, New Jersey: Lawrence Erlbaum Associates, Inc.

Philippot, P., & Brutoux, F. (2008). Induced rumination dampens executive processes in dysphoric young adults. *Journal of Behavior Therapy and Experimental Psychiatry, 39*(3), 219-227.

Pickles, A., Rowe, R., Simonoff, E., Foley, D., Rutter, M., & Silberg, J. (2001). Child psychiatric symptoms and psychosocial impairment: relationship and prognostic significance. *British Journal of Psychiatry, 179*, 230-235.

Piet, J., & Hougaard, E. (2011). The effect of mindfulness-based cognitive therapy for prevention of relapse in recurrent major depressive disorder: a systematic review and meta-analysis. *Clinical psychology review, 31*(6), 1032-1040.

Piet, J., Hougaard, E., Hecksher, M. S., & Rosenberg, N. K. (2010). A randomized pilot study of mindfulness-based cognitive therapy and group cognitive-behavioral therapy for young adults with social phobia. *Scandinavian Journal of Psychology, 51*(5), 403-410.

Pine, D. S., Cohen, B. H., Gurley, D., Brook, J., & Ma, J. (1998). The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Archives of General Psychiatry, 55*, 56-64.

Pine, D. S., Mogg, K., Bradley, B. P., Montgomery, L., Monk, C. S., McClure, E., . . . Kaufman, J. (2005). Attention bias to threat in maltreated children: Implications for vulnerability to stress-related psychopathology. *American Journal of Psychiatry, 162*(2), 291-296.

Plaisier, I., Beekman, A., De Graaf, R., Smit, J., Van Dyck, R., & Penninx, B. (2010). Work functioning in persons with depressive and anxiety disorders: the role of specific psychopathological characteristics. *Journal of Affective Disorders, 125*(1), 198-206.

Plomin, R., DeFries, J. C., Knopik, V. S., & Neiderhiser, J. M. (2013). *Behavioral Genetics* (6th ed.). New York: Worth Publishers.

Plomin, R., Haworth, C. M., & Davis, O. S. (2009). Common disorders are quantitative traits. *Nature Reviews: Genetics, 10*(12), 872-878.

Plomin, R., & Kovas, Y. (2005). Generalist genes and learning disabilities. *Psychological Bulletin, 131*, 592-617.

Plomin, R., Willerman, L., & Loehlin, J. C. (1976). Resemblance in appearance and the equal environments assumption in twin studies of personality. *Behavior Genetics, 6*, 43-52.

Pollak, S. D. (2003). Experience-Dependent Affective Learning and Risk for Psychopathology in Children. *Annals of the New York Academy of Sciences, 1008*(1), 102-111.

Pollak, S. D., Cicchetti, D., Hornung, K., & Reed, A. (2000). Recognizing emotion in faces: developmental effects of child abuse and neglect. *Developmental Psychology, 36*(5), 679.

Posner, M. I., & Petersen, S. E. (1990). The attention system of the human brain. *Annual Review of Neuroscience, 13*, 25-42.

Pössel, P., Seemann, S., & Hautzinger, M. (2008). Impact of comorbidity in prevention of adolescent depressive symptoms. *Journal of Counseling Psychology, 55*(1), 106.

Prenoveau, J. M., Zinbarg, R. E., Craske, M. G., Mineka, S., Griffith, J. W., & Epstein, A. M. (2010). Testing a hierarchical model of anxiety and depression in adolescents: A tri-level model. *Journal of Anxiety Disorders, 24*(3), 334-344.

Price, T. S., Freeman, B., Craig, I. W., Petrill, S. A., Ebersole, L., & Plomin, R. (2000). Infant zygosity can be assigned by parental report questionnaire data. *Twin Research, 3*, 129-133.

Puig-Antich, J., Kaufman, J., Ryan, N. D., Williamson, D. E., Dahl, R. E., Lukens, E., . . . Nelson, B. (1993). The psychosocial functioning and family environment of depressed adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry, 32*, 244-253.

Rabian, B., Embry, L., & MacIntyre, D. (1999). Behavioral validation of the Childhood Anxiety Sensitivity Index in children. *Journal of Clinical Child Psychology, 28*(1), 105-112.

Raes, F., & Williams, J. M. G. (2010). The relationship between mindfulness and uncontrollability of ruminative thinking. *Mindfulness, 1*(4), 199-203.

Raes, F., Williams, J. M. G., & Hermans, D. (2009). Reducing cognitive vulnerability to depression: A preliminary investigation of MEmory Specificity Training (MEST) in inpatients with depressive symptomatology. *Journal of Behavior Therapy and Experimental Psychiatry, 40*(1), 24-38.

Rapee, R. M. (1997). Potential role of childrearing practices in the development of anxiety and depression. *Clinical psychology review, 17*, 47-67.

Rapee, R. M., Lyneham, H. J., Hudson, J. L., Kangas, M., Wuthrich, V. M., & Schniering, C. A. (2013). Effect of comorbidity on treatment of anxious children and adolescents: results from a large, combined sample. *Journal of the American Academy of Child and Adolescent Psychiatry, 52*(1), 47-56.

Rector, N. A., Szacun-Shimizu, K., & Leybman, M. (2007). Anxiety sensitivity within the anxiety disorders: Disorder-specific sensitivities and depression comorbidity. *Behaviour Research and Therapy, 45*(8), 1967-1975.

Reich, J. (1995). Family psychiatric histories in male patients with generalized anxiety disorder and major depressive disorder. *Annals of Clinical Psychiatry, 7*(2), 71-78.

Reid, S. C., Salmon, K., & Lovibond, P. F. (2006). Cognitive biases in childhood anxiety, depression, and aggression: Are they pervasive or specific? *Cognitive Therapy and Research, 30*(5), 531-549.

Reinholdt-Dunne, M. L., Mogg, K., & Bradley, B. P. (2009). Effects of anxiety and attention control on processing pictorial and linguistic emotional information. *Behaviour Research and Therapy, 47*(5), 410-417.

Reiss, S., Peterson, R. A., Gursky, D. M., & McNally, R. J. (1986). Anxiety sensitivity, anxiety frequency and the predictions of fearfulness. *Behaviour Research and Therapy, 24*(1), 1-8.

Reppermund, S., Ising, M., Lucae, S., & Zihl, J. (2009). Cognitive impairment in unipolar depression is persistent and non-specific: further evidence for the final common pathway disorder hypothesis. *Psychological Medicine, 39*(04), 603-614.

Rhew, I. C., Simpson, K., Tracy, M., Lymp, J., McCauley, E., Tsuang, D., & Stoep, A. V. (2010). Criterion validity of the Short Mood and Feelings Questionnaire and one-and two-item depression screens in young adolescents. *Child and adolescent psychiatry and mental health, 4*(8), 1-11.

Rice, F., Harold, G. T., Shelton, K. H., Thapar, A., Rice, F., Harold, G. T., . . . Thapar, A. (2006). Family conflict interacts with genetic liability in predicting childhood and adolescent depression. *Journal of the American Academy of Child and Adolescent Psychiatry, 45*(7), 841-848.

Rice, F., Harold, G. T., & Thapar, A. (2002a). Assessing the effects of age, sex and shared environment on the genetic aetiology of depression in childhood and adolescence. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 43*(8), 1039-1051.

Rice, F., Harold, G. T., & Thapar, A. (2002b). The genetic aetiology of childhood depression: A review. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 43*(1), 65-80.

Rice, F., Harold, G. T., & Thapar, A. (2003). Negative life events as an account of age-related differences in the genetic aetiology of depression in childhood and adolescence. *Journal of child psychology and psychiatry, 44*(7), 977-987.

Rice, F., van den Bree, M. B., & Thapar, A. (2004). A population-based study of anxiety as a precursor for depression in childhood and adolescence. *BMC psychiatry, 4*(1), 43.

Richards, J. C., Austin, D. W., & Alvarenga, M. E. (2001). Interpretation of ambiguous interoceptive stimuli in panic disorder and nonclinical panic. *Cognitive Therapy and Research, 25*(3), 235-246.

Richey, J. A., Keough, M. E., & Schmidt, N. B. (2012). Attentional control moderates fearful responding to a 35% CO 2 Challenge. *Behavior Therapy, 43*(2), 285-299.

Riglin, L., Petrides, K., Frederickson, N., & Rice, F. (2014). The relationship between emotional problems and subsequent school attainment: A meta-analysis. *Journal of Adolescence, 37*(4), 335-346.

Rijsdijk, F. (2005a). Common pathway model. In B. S. Everitt & D. C. Howell (Eds.), *Encyclopedia of Statistics in Behavioral Science*. Chichester: John Wiley & Sons, Ltd.

Rijsdijk, F. (2005b). Independent pathway model. In B. S. Everitt & D. C. Howell (Eds.), *Encyclopedia of Statistics in Behavioral Science*. Chichester: John Wiley & Sons, Ltd.

Rijsdijk, F. V., & Sham, P. C. (2002). Analytic approaches to twin data using structural equation models. *Briefings in bioinformatics, 3* 119-133.

Rinck, M., Becker, E. S., Kellermann, J., & Roth, W. T. (2003). Selective attention in anxiety: Distraction and enhancement in visual search. *Depression and anxiety, 18*(1), 18-28.

Rinck, M., Reinecke, A., Ellwart, T., Heuer, K., & Becker, E. S. (2005). Speeded detection and increased distraction in fear of spiders: evidence from eye movements. *Journal of Abnormal Psychology, 114*(2), 235.

Ripke, S., Wray, N. R., Lewis, C. M., Hamilton, S. P., Weissman, M. M., Breen, G., . . . Cichon, S. (2013). A mega-analysis of genome-wide association studies for major depressive disorder. *Molecular Psychiatry, 18*(4), 497-511.

Robbers, S. C. C., Bartels, M., van Oort, F. V. A., van Beijsterveldt, C. E. M., van der Ende, J., Verhulst, F. C., . . . Huizink, A. C. (2010). A Twin-Singleton Comparison of Developmental Trajectories of Externalizing and Internalizing Problems in 6-to 12-Year-Old Children. *Twin Research and Human Genetics, 13*(1), 79-87. Retrieved from <Go to ISI>://WOS:000275258400008

Roberson-Nay, R., Eaves, L. J., Hettema, J. M., Kendler, K. S., & Silberg, J. L. (2012). Childhood separation anxiety disorder and adult onset panic attacks share a common genetic diathesis. *Depression and anxiety, 29*(4), 320-327.

Rock, P., Roiser, J., Riedel, W., & Blackwell, A. (2014). Cognitive impairment in depression: a systematic review and meta-analysis. *Psychological Medicine, 44*(10), 2029-2040.

Rodriguez, B. F., Bruce, S. E., Pagano, M. E., Spencer, M. A., & Keller, M. B. (2004). Factor structure and stability of the Anxiety Sensitivity Index in a longitudinal study of anxiety disorder patients. *Behaviour Research and Therapy, 42*(1), 79-91.

Roelofs, J., Rood, L., Meesters, C., Te Dorsthorst, V., Bögels, S., Alloy, L. B., & Nolen-Hoeksema, S. (2009). The influence of rumination and distraction on depressed and anxious mood: A prospective examination of the response styles theory in children and adolescents. *European Child and Adolescent Psychiatry, 18*(10), 635-642.

Rohde, P., Clarke, G. N., Lewinsohn, P. M., Seeley, J. R., & Kaufman, N. K. (2001). Impact of comorbidity on a cognitive-behavioral group treatment for adolescent depression. *Journal of the American Academy of Child and Adolescent Psychiatry, 40*(7), 795-802.

Rohde, P., Lewinsohn, P. M., & Seeley, J. R. (1990). Are people changed by the experience of having an episode of depression? A further test of the scar hypothesis. *Journal of Abnormal Psychology, 99*(3), 264.

Ronald, A. (2011). Is the child 'father of the Man'? Evaluating the stability of genetic influences across development. *Developmental Science, 14*(6), 1471-1478.

Rood, L., Roelofs, J., Bögels, S. M., Nolen-Hoeksema, S., & Schouten, E. (2009). The influence of emotion-focused rumination and distraction on depressive symptoms in non-clinical youth: A meta-analytic review. *Clinical psychology review, 29*(7), 607-616.

Roughan, L., & Hadwin, J. A. (2011). The impact of working memory training in young people with social, emotional and behavioural difficulties. *Learning and Individual Differences, 21*(6), 759-764.

Rowe, R., Rijsdijk, F. V., Maughan, B., Hosang, G. M., & Eley, T. C. (2008). Heterogeneity in antisocial behaviours and comorbidity with depressed mood: A behavioural genetic approach. *Journal of Child Psychology & Psychiatry, 49*(5), 526-534.

Roy, M. A., Neale, M. C., Pedersen, N. L., Mathe, A. A., & Kendler, K. S. (1995). A twin study of generalized anxiety disorder and major depression. *Psychological Medicine, 25*(5), 1037-1049.

Røysamb, E., Kendler, K. S., Tambs, K., Ørstavik, R. E., Neale, M. C., Aggen, S. H., . . . Reichborn-Kjennerud, T. (2011). The joint structure of DSM-IV Axis I and Axis II disorders. *Journal of Abnormal Psychology, 120*(1), 198.

Rutter, M. (1994). Comorbidity: Meanings and mechanisms. *Clinical psychology: Science and practice, 1*, 100-103.

Rutter, M. (1997). Comorbidity: concepts, claims and choices. *Criminal Behaviour and Mental Health, 7*(4), 265-285.

Rutter, M., Kim-Cohen, J., & Maughan, B. (2006). Continuities and discontinuities in psychopathology between childhood and adult life. *Journal of child psychology and psychiatry, 47*, 276-295.

Rutter, M., & Redshaw, J. (1991). Annotation: Growing up as a twin: Twin-singleton differences in psychological development. *Journal of child psychology and psychiatry, 32*(6), 885-895.

Salemink, E., & Wiers, R. W. (2012). Adolescent threat-related interpretive bias and its modification: The moderating role of regulatory control. *Behaviour Research and Therapy, 50*(1), 40-46.

Salum, G., Mogg, K., Bradley, B., Gadelha, A., Pan, P., Tamanaha, A., . . . Polanczyk, G. (2013). Threat bias in attention orienting: evidence of specificity in a large community-based study. *Psychological Medicine, 43*(04), 733-745.

Scaini, S., Belotti, R., & Ogliari, A. (2014). Genetic and environmental contributions to social anxiety across different ages: A meta-analytic approach to twin data. *Journal of Anxiety Disorders, 28*(7), 650-656.

Scaini, S., Ogliari, A., Eley, T. C., Zavos, H., & Battaglia, M. (2012). Genetic and environmental contributions to separation anxiety: a meta-analytic approach to twin data. *Depression and anxiety, 29*(9), 754-761.

Schmidt, N. B., Keough, M. E., Mitchell, M. A., Reynolds, E. K., MacPherson, L., Zvolensky, M. J., & Lejuez, C. (2010). Anxiety sensitivity: Prospective prediction of anxiety among early adolescents. *Journal of Anxiety Disorders, 24*(5), 503-508.

Schmidt, N. B., Lerew, D. R., & Joiner Jr, T. E. (2000). Prospective evaluation of the etiology of anxiety sensitivity: test of a scar model. *Behaviour Research and Therapy, 38*(11), 1083-1095. Retrieved from http://www.sciencedirect.com/science/article/pii/S0005796799001382

Schmidt, N. B., Lerew, D. R., & Joiner, T. E., Jr. (1998). Anxiety sensitivity and the pathogenesis of anxiety and depression: evidence for symptom specificity. *Behaviour Research and Therapy, 36*(2), 165-177.

Schmidt, N. B., Zvolensky, M. J., & Maner, J. K. (2006). Anxiety sensitivity: prospective prediction of panic attacks and Axis I pathology. *Journal of Psychiatric Research, 40*(8), 691-699.

Schmukle, S. C. (2005). Unreliability of the dot probe task. *European Journal of Personality, 19*(7), 595-605.

Schumacher, J., Kristensen, A. S., Wendland, J. R., Nöthen, M. M., Mors, O., & McMahon, F. J. (2011). The genetics of panic disorder. *Journal of Medical Genetics, 48*(6), 361-368.

Scott, A., Pearce, D., & Goldblatt, P. (2001). The sizes and characteristics of the minority ethnic populations of Great Britain-latest estimates. *Population Trends, 105*, 6-15.

Scourfield, J., Rice, F., Thapar, A., Harold, G. T., Martin, N., & McGuffin, P. (2003). Depressive symptoms in children and adolescents: changing aetiological influences with development. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 44*(7), 968-976.

Sebire, N. J., Snijders, R. J., Hughes, K., Sepulveda, W., & Nicolaides, K. H. (1997). The hidden mortality of monochorionic twin pregnancies. *BJOG: An International Journal of Obstetrics & Gynaecology, 104*(10), 1203-1207.

Seeley, J. R., Kosty, D. B., Farmer, R. F., & Lewinsohn, P. M. (2011). The modeling of internalizing disorders on the basis of patterns of lifetime comorbidity: Associations with psychosocial functioning and psychiatric disorders among first-degree relatives. *Journal of Abnormal Psychology, 120*(2), 308-321.

Sellbom, M., Ben-Porath, Y. S., & Bagby, R. M. (2008). On the hierarchical structure of mood and anxiety disorders: Confirmatory evidence and elaboration of a model of temperament markers. *Journal of Abnormal Psychology, 117*(3), 576-590.

Shahar, B., Britton, W. B., Sbarra, D. A., Figueredo, A. J., & Bootzin, R. R. (2010). Mechanisms of change in mindfulness-based cognitive therapy for depression: Preliminary evidence

from a randomized controlled trial. *International Journal of Cognitive Therapy, 3*(4), 402-418.

Sham, P. C., Sterne, A., Purcell, S., Cherny, S. S., Webster, M., Rijsdijk, F. V., . . . Plomin, R. (2000). GENESiS: Creating a composite index of the vulnerability to anxiety and depression in a community-based sample of siblings. *Twin Research, 3*(4), 316-322.

Shear, K., Jin, R., Ruscio, A., Walters, E., & Kessler, R. (2006). Prevalence and correlates of estimated DSM-IV child and adult separation anxiety disorder in the National Comorbidity Survey Replication. *American Journal of Psychiatry, 163*(6), 1074-1083.

Shih, R. A., Belmonte, P. L., & Zandi, P. P. (2004). A review of the evidence from family, twin and adoption studies for a genetic contribution to adult psychiatric disorders. *International Review of Psychiatry, 16*(4), 260-283.

Shimada-Sugimoto, M., Otowa, T., & Hettema, J. M. (2015). Genetics of anxiety disorders: Genetic epidemiological and molecular studies in humans. *Psychiatry and Clinical Neurosciences*.

Shipstead, Z., Hicks, K. L., & Engle, R. W. (2012). Cogmed working memory training: Does the evidence support the claims? *Journal of Applied Research in Memory and Cognition, 1*(3), 185-193.

Siegle, G. J., Ghinassi, F., & Thase, M. E. (2007). Neurobehavioral therapies in the 21st century: Summary of an emerging field and an extended example of cognitive control training for depression. *Cognitive Therapy and Research, 31*(2), 235-262.

Silberg, J. L., & Bulik, C. M. (2005). The developmental association between eating disorders symptoms and symptoms of depression and anxiety in juvenile twin girls. *Journal of child psychology and psychiatry, 46*(12), 1317-1326.

Silberg, J. L., Rutter, M., & Eaves, L. (2001). Genetic and environmental influences on the temporal association between earlier anxiety and later depression in girls. [erratum

appears in Biol Psychiatry 2001 Sep 1;50(5):393.]. *Biological Psychiatry, 49*(12), 1040-1049.

Silverman, W. K., Fleisig, W., Rabian, B., & Peterson, R. A. (1991). Childhood anxiety sensitivity index. *Journal of Clinical Child Psychology, 20*(2), 162-168.

Simms, L., Prisciandaro, J., Krueger, R., & Goldberg, D. (2012). The structure of depression, anxiety and somatic symptoms in primary care. *Psychological Medicine, 42*(01), 15-28.

Simms, L. J., Grös, D. F., Watson, D., & O'Hara, M. W. (2008). Parsing the general and specific components of depression and anxiety with bifactor modeling. *Depression and anxiety, 25*(7), E34-E46.

Simon, N. M., Otto, M. W., Smits, J. A. J., Nicolaou, D. C., Reese, H. E., & Pollack, M. H. (2004). Changes in anxiety sensitivity with pharmacotherapy for panic disorder. *Journal of Psychiatric Research, 38*(5), 491-495. Retrieved from http://www.sciencedirect.com/science/article/pii/S0022395604000202

Simonoff, E. (1992). A comparison of twins and singletons with child psychiatric disorders: an Item Sheet study. *Journal of child psychology and psychiatry, 33*(8), 1319-1332.

Skirbekk, B., Hansen, B. H., Oerbeck, B., Wentzel-Larsen, T., & Kristensen, H. (2012). Motor impairment in children with anxiety disorders. *Psychiatry Research, 198*(1), 135-139.

Skre, I., Onstad, S., Edvardsen, J., Torgersen, S., & Kringlen, E. (1994). A family study of anxiety disorders: familial transmission and relationship to mood disorder and psychoactive substance use disorder. *Acta Psychiatrica Scandinavica, 90*(5), 366-374.

Slade, T., & Watson, D. (2006). The structure of common DSM-IV and ICD-10 mental disorders in the Australian general population. *Psychological Medicine, 36*(11), 1593-1600.

Smith, D. J., Muir, W. J., & Blackwood, D. H. (2006). Neurocognitive impairment in euthymic young adults with bipolar spectrum disorder and recurrent major depressive disorder. *Bipolar Disorders, 8*(1), 40-46.

Smits, J. A., Powers, M. B., Cho, Y., & Telch, M. J. (2004). Mechanism of change in cognitive-behavioral treatment of panic disorder: evidence for the fear of fear mediational hypothesis. *Journal of consulting and clinical psychology, 72*(4), 646-652. Retrieved from http://ukpmc.ac.uk/abstract/MED/15301649

Snyder, H. R. (2013). Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: A meta-analysis and review. *Psychological Bulletin, 139*(1), 81-132.

Snyder, H. R., Miyake, A., & Hankin, B. L. (2015). Advancing understanding of executive function impairments and psychopathology: bridging the gap between clinical and cognitive approaches. *Frontiers in Psychology, 6*.

Spence, S. H. (1998). A measure of anxiety symptoms among children. *Behaviour Research and Therapy, 36*(5), 545-566.

Spielberger, C. (1973). *Preliminary test manual for the State-Trait Anxiety Inventory for Children*. Palo Alto: Consulting Psychologists Press, Inc.

Starcevic, V., Berle, D., Milicevic, D., Hannan, A., Lamplugh, C., & Eslick, G. D. (2007). Pathological worry, anxiety disorders and the impact of co-occurrence with depressive and other anxiety disorders. *Journal of Anxiety Disorders, 21*(8), 1016-1027.

Stark, K. D., & Laurent, J. (2001). Joint factor analysis of the children's depression inventory and the revised children's manifest anxiety scale. *Journal of Clinical Child Psychology, 30*(4), 552-567.

Starr, L., Conway, C., Hammen, C., & Brennan, P. (2013). Transdiagnostic and disorder-specific models of intergenerational transmission of internalizing pathology. *Psychological Medicine*, 1-12.

Starr, L. R., & Davila, J. (2012). Temporal patterns of anxious and depressed mood in generalized anxiety disorder: A daily diary study. *Behaviour Research and Therapy, 50*(2), 131-141.

Stein, M. B., Jang, K. L., & Livesley, W. J. (1999). Heritability of anxiety sensitivity: A twin study. *American Journal of Psychiatry, 156*(2), 246-251.

Stein, M. B., Schork, N. J., Gelernter, J., Stein, M. B., Schork, N. J., & Gelernter, J. (2008). Gene-by-environment (serotonin transporter and childhood maltreatment) interaction for anxiety sensitivity, an intermediate phenotype for anxiety disorders. *Neuropsychopharmacology, 33*(2), 312-319.

Stone, L. B., McGeary, J. E., Palmer, R. H., & Gibb, B. E. (2013). Identifying genetic predictors of depression risk: 5-HTTLPR and BDNF Val66Met polymorphisms are associated with rumination and co-rumination in adolescents. *Frontiers in genetics, 4*, 246.

Strauss, G. P., Allen, D. N., Jorgensen, M. L., & Cramer, S. L. (2005). Test-retest reliability of standard and emotional stroop tasks an investigation of color-word and picture-word versions. *Assessment, 12*(3), 330-337.

Subbarao, A., Rhee, S. H., Young, S. E., Ehringer, M. A., Corley, R. P., & Hewitt, J. K. (2008). Common genetic and environmental influences on major depressive disorder and conduct disorder. *Journal of Abnormal Child Psychology, 36*(3), 433-444.

Sugiura, Y. (2004). Detached mindfulness and worry: a meta-cognitive analysis. *Personality and Individual Differences, 37*(1), 169-179.

Sullivan, P. F., Neale, M. C., & Kendler, K. S. (2000). Genetic epidemiology of major depression: review and meta-analysis. *American Journal of Psychiatry, 157*(10), 1552-1562.

Susa, G., Pitică, I., Benga, O., & Miclea, M. (2012). The self regulatory effect of attentional control in modulating the relationship between attentional biases toward threat and anxiety symptoms in children. *Cognition & emotion, 26*(6), 1069-1083.

Taghavi, M. R., Neshat-Doost, H. T., Moradi, A. R., Yule, W., & Dalgleish, T. (1999). Biases in visual attention in children and adolescents with clinical anxiety and mixed anxiety-depression. *Journal of Abnormal Child Psychology, 27*(3), 215-223.

Tanay, G., Lotan, G., & Bernstein, A. (2012). Salutary proximal processes and distal mood and anxiety vulnerability outcomes of mindfulness training: A pilot preventive intervention. *Behavior Therapy, 43*(3), 492-505.

Tao, R., Emslie, G., Mayes, T., Nakonezny, P., Kennard, B., & Hughes, C. (2009). Early prediction of acute antidepressant treatment response and remission in pediatric major depressive disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 48*(1), 71-78.

Taylor, S. (1996). Nature and measurement of anxiety sensitivity: Reply to Lilienfeld, Turner, and Jacob (1996). *Journal of Anxiety Disorders, 10*(5), 425-451.

Taylor, S. (1999). *Anxiety Sensitivity*. Mahwah, NJ: Lawrence Erlbaum Associates.

Taylor, S. (2003). Anxiety Sensitivity and Its Implications for Understanding and Treating PTSD. *Journal of Cognitive Psychotherapy, 17*(2), 179-186. Retrieved from http://www.ingentaconnect.com/content/springer/jcogp/2003/00000017/00000002/art00008

http://dx.doi.org/10.1891/jcop.17.2.179.57431

Taylor, S., & Fedoroff, I. C. (1999). The Expectancy Theory of Fear, Anxiety and Panic: A conceptual and empirical analysis. In S. Taylor (Ed.), *Anxiety Sensitivity: Theory, research and treatment of the fear of anxiety*. London: Lawrence Erlbaum.

Taylor, S., Jang, K. L., Stewart, S. H., Stein, M. B., Taylor, S., Jang, K. L., . . . Stein, M. B. (2008). Etiology of the dimensions of anxiety sensitivity: a behavioral-genetic analysis. *Journal of Anxiety Disorders, 22*(5), 899-914.

Taylor, S., Koch, W. J., Woody, S., & McLean, P. (1996). Anxiety sensitivity and depression: how are they related? *Journal of Abnormal Psychology, 105*(3), 474.

TeamRDC. (2010). R: A Language and Environment for Statistical Computing. *R Foundation for Statistical Computing. Vienna Austria.*

Thapar, A., Collishaw, S., Pine, D. S., & Thapar, A. K. (2012). Depression in adolescence. *The Lancet, 379*(9820), 1056-1067.

Thapar, A., & McGuffin, P. (1997). Anxiety and depressive symptoms in childhood - a genetic study of comorbidity. *Journal of child psychology and psychiatry, 38*(6), 651-656.

Thapar, A., & Rice, F. (2006). Twin studies in pediatric depression. *Child and Adolescent Psychiatric Clinics of North America, 15*(4), 869-881, viii.

Theeuwes, J. (1991). Cross-dimensional perceptual selectivity. *Perception and Psychophysics, 50*(2), 184-193.

Theeuwes, J. (1992). Perceptual selectivity for color and form. *Perception and Psychophysics, 51*(6), 599-606.

Theeuwes, J. (2010). Top–down and bottom–up control of visual selection. *Acta Psychologica, 135*(2), 77-99.

Thomas, A., Gallagher, P., Robinson, L., Porter, R., Young, A., Ferrier, I., & O'Brien, J. (2009). A comparison of neurocognitive impairment in younger and older adults with major depression. *Psychological Medicine, 39*(05), 725-733.

Thomason, M. E., Henry, M. L., Hamilton, J. P., Joormann, J., Pine, D. S., Ernst, M., . . . Gotlib, I. H. (2010). Neural and behavioral responses to threatening emotion faces in children as a function of the short allele of the serotonin transporter gene. *Biological Psychology, 85*(1), 38-44. doi:10.1016/j.biopsycho.2010.04.009

Titov, N., Dear, B. F., Schwencke, G., Andrews, G., Johnston, L., Craske, M. G., & McEvoy, P. (2011). Transdiagnostic internet treatment for anxiety and depression: A randomised controlled trial. *Behaviour Research and Therapy, 49*(8), 441-452. Retrieved from http://www.sciencedirect.com/science/article/pii/S0005796711000799

Traylor, M., Markus, H., & Lewis, C. M. (2014). Homogeneous case subgroups increase power in genetic association studies. *European Journal of Human Genetics*, 1-7. doi:doi: 10.1038/ejhg.2014.194

Trosper, S. E., Whitton, S. W., Brown, T. A., & Pincus, D. B. (2012). Understanding the latent structure of the emotional disorders in children and adolescents. *Journal of Abnormal Child Psychology, 40*(4), 621-632.

Trouton, A., Spinath, F. M., & Plomin, R. (2002). Twins Early Development Study (TEDS): A multivariate, longitudinal genetic investigation of language, cognition and behaviour problems in childhood. *Twin Research, 5*(5), 444-448.

Trzaskowski, M., Eley, T. C., Davis, O. S., Doherty, S. J., Hanscombe, K. B., Meaburn, E. L., . . . Plomin, R. (2013). First genome-wide association study on anxiety-related behaviours in childhood. *PloS one, 8*(4), e58676.

Trzaskowski, M., Zavos, H., Haworth, C., Plomin, R., & Eley, T. (2011). Stable Genetic Influence on Anxiety-Related Behaviours Across Middle Childhood. *Journal of Abnormal Child Psychology, 40*(1), 85-94. doi:10.1007/s10802-011-9545-z

Tull, M. T., & Gratz, K. L. (2008). Further examination of the relationship between anxiety sensitivity and depression: The mediating role of experiential avoidance and difficulties engaging in goal-directed behavior when distressed. *Journal of Anxiety Disorders, 22*(2), 199-210.

Tully, E. C., Iacono, W. G., & McGue, M. (2010). Changes in genetic and environmental influences on the development of nicotine dependence and major depressive disorder from middle adolescence to early adulthood. *Development and Psychopathology, 22*(04), 831-848.

Tully, P. J., Zajac, I. T., & Venning, A. J. (2009). The structure of anxiety and depression in a normative sample of younger and older Australian adolescents. *Journal of Abnormal Child Psychology, 37*(5), 717-726.

Ursache, A., & Raver, C. C. (2014). Trait and state anxiety: Relations to executive functioning in an at-risk sample. *Cognition & emotion, 28*(5), 845-855.

Valentine, E. R., & Sweet, P. L. (1999). Meditation and attention: A comparison of the effects of concentrative and mindfulness meditation on sustained attention. *Mental Health, Religion & Culture, 2*(1), 59-70.

Van Aalderen, J., Donders, A., Giommi, F., Spinhoven, P., Barendregt, H., & Speckens, A. (2012). The efficacy of mindfulness-based cognitive therapy in recurrent depressed patients with and without a current depressive episode: a randomized controlled trial. *Psychological Medicine, 42*(05), 989-1001.

Van Ameringen, M., Mancini, C., & Farvolden, P. (2003). The impact of anxiety disorders on educational achievement. *Journal of Anxiety Disorders, 17*(5), 561-571.

Van Bockstaele, B., Verschuere, B., Tibboel, H., De Houwer, J., Crombez, G., & Koster, E. H. (2014). A review of current evidence for the causal impact of attentional bias on fear and anxiety. *Psychological Bulletin, 140*(3), 682.

Van Dam, N. T., Earleywine, M., & Borders, A. (2010). Measuring mindfulness? An item response theory analysis of the mindful attention awareness scale. *Personality and Individual Differences, 49*(7), 805-810.

van der Velden, A. M., Kuyken, W., Wattar, U., Crane, C., Pallesen, K. J., Dahlgaard, J., . . . Piet, J. (2015). A systematic review of mechanisms of change in mindfulness-based cognitive therapy in the treatment of recurrent major depressive disorder. *Clinical psychology review, 37*, 26-39.

Van Houtem, C., Laine, M., Boomsma, D., Ligthart, L., Van Wijk, A., & De Jongh, A. (2013). A review and meta-analysis of the heritability of specific phobia subtypes and corresponding fears. *Journal of Anxiety Disorders, 27*(4), 379-388.

Van Vugt, M. K., Hitchcock, P., Shahar, B., & Britton, W. (2012). The effects of mindfulness-based cognitive therapy on affective memory recall dynamics in depression: a mechanistic model of rumination. *Frontiers in human neuroscience, 6*.

Verona, E., Javdani, S., & Sprague, J. (2011). Comparing factor structures of adolescent psychopathology. *Psychological Assessment, 23*(2), 545.

Verstraeten, K., Bijttebier, P., Vasey, M. W., & Raes, F. (2011). Specificity of worry and rumination in the development of anxiety and depressive symptoms in children. *British Journal of Clinical Psychology, 50*(4), 364-378.

Verstraeten, K., Vasey, M. W., Raes, F., & Bijttebier, P. (2009). Temperament and risk for depressive symptoms in adolescence: Mediation by rumination and moderation by effortful control. *Journal of Abnormal Child Psychology, 37*(3), 349-361.

Viana, A. G., & Rabian, B. (2009). Fears of cognitive dyscontrol and publicly observable anxiety symptoms: Depression predictors in moderate-to-high worriers. *Journal of Anxiety Disorders, 23*(8), 1126-1131.

Visu-Petra, L., Cheie, L., Benga, O., & Alloway, T. P. (2011). Effects of anxiety on memory storage and updating in young children. *International Journal of Behavioral Development, 35*(1), 38-47.

Vitiello, B., & Research Units on Pediatric Psychopharmacology Anxiety Study Group. (2003). Searching for moderators and mediators of pharmacological treatment effects in children and adolescents with anxiety disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 42*(1), 13-21.

Vollebergh, W. A., Iedema, J., Bijl, R. V., de Graaf, R., Smit, F., & Ormel, J. (2001). The structure and stability of common mental disorders: the NEMESIS study. *Archives of General Psychiatry, 58*(6), 597-603.

Vujanovic, A. A., Zvolensky, M. J., Bernstein, A., Feldner, M. T., & McLeish, A. C. (2007). A test of the interactive effects of anxiety sensitivity and mindfulness in the prediction of anxious arousal, agoraphobic cognitions, and body vigilance. *Behaviour Research and Therapy, 45*(6), 1393-1400.

Wagenmakers, E.-J., & Farrell, S. (2004). AIC model selection using Akaike weights. *Psychonomic bulletin & review, 11*(1), 192-196.

Waghorn, G., Chant, D., White, P., & Whiteford, H. (2005). Disability, employment and work performance among people with ICD-10 anxiety disorders. *Australian and New Zealand Journal of Psychiatry, 39*(1-2), 55-66.

Ward, R. (2013). *Maternal and paternal employment rates by age of youngest dependent child in the family unit, April-June 2012.* . Retrieved from The Department for Work and Pensions:

Wass, S., Scerif, G., & Johnson, M. H. (2012). Training attentional control and working memory–Is younger, better? *Developmental Review, 32*(4), 360-387.

Waszczuk, M. A., Zavos, H. M. S., & Eley, T. C. (2013). Genetic and Environmental Influences on Relationship between Anxiety Sensitivity and Anxiety Subscales in Children. *Journal of Anxiety Disorders, 27*(5), 475-484.

Waters, A. M., Bradley, B., & Mogg, K. (2014). Biased attention to threat in paediatric anxiety disorders (generalized anxiety disorder, social phobia, specific phobia, separation anxiety disorder) as a function of 'distress' versus 'fear'diagnostic categorization. *Psychological Medicine, 44*(03), 607-616.

Watkins, E., & Brown, R. (2002). Rumination and executive function in depression: An experimental study. *Journal of Neurology, Neurosurgery and Psychiatry, 72*(3), 400-402.

Watson, D. (2005). Rethinking the Mood and Anxiety Disorders: A Quantitative Hierarchical Model for DSM–V. *Journal of Abnormal Psychology, 114*(4), 522-536.

Watson, D. (2009). Differentiating the mood and anxiety disorders: A quadripartite model. *Annual Review of Clinical Psychology, 5*, 221-247.

Watson, D., Clark, L. A., Weber, K., Smith Assenheimer, J., Strauss, M. E., & McCormick, R. A. (1995a). Testing a Tripartite Model: I. Evaluating the convergent and discriminant

validity of anxiety and depression symptom scales. *Journal of Abnormal Psychology, 104*, 3-14.

Watson, D., Clark, L. A., Weber, K., Smith Assenheimer, J., Strauss, M. E., & McCormick, R. A. (1995b). Testing a Tripartite Model: II. Exploring the symptom structure of anxiety and depression in student, adult, and patient samples. *Journal of Abnormal Psychology, 104*(1), 15-25.

Watts, S. E., & Weems, C. F. (2006). Associations among selective attention, memory bias, cognitive errors and symptoms of anxiety in youth. *Journal of Abnormal Child Psychology, 34*(6), 838-849.

Weems, C. F., Hammond-Laurence, K., Silverman, W. K., & Ferguson, C. (1997). The relation between anxiety sensitivity and depression in children and adolescents referred for anxiety. *Behaviour Research and Therapy, 35*, 961-966.

Weems, C. F., Hammond-Laurence, K., Silverman, W. K., & Ginsburg, G. S. (1998). Testing the utility of the anxiety sensitivity construct in children and adolescents referred for anxiety disorders. *Journal of Clinical Child Psychology, 27*, 69-77.

Weems, C. F., Hayward, C., Killen, J., & Taylor, C. B. (2002). A longitudinal investigation of anxiety sensitivity in adolescence. *Journal of Abnormal Psychology, 111*(3), 471.

Weersing, V. R., Rozenman, M. S., Maher-Bridge, M., & Campo, J. V. (2012). Anxiety, depression, and somatic distress: Developing a transdiagnostic internalizing toolbox for pediatric practice. *Cognitive and behavioral practice, 19*(1), 68-82.

Weissman, M. M., Leckman, J. F., Merikangas, K. R., Gammon, G. D., & Prusoff, B. A. (1984). Depression and Anxiety Disorders in Parents and Children: Results From the Yale Family Study. *Archives of General Psychiatry, 41*(9), 845-852. doi:10.1001/archpsyc.1984.01790200027004

Weissman, M. M., Wickramaratne, P., Adams, P. B., Lish, J. D., Horwath, E., Charney, D., . . . Frosch, E. (1993). The relationship between panic disorder and major depression. A new family study. *Archives of General Psychiatry, 50*(10), 767-780.

Wertz, J., Zavos, H., Matthews, T., Harvey, K., Hunt, A., Pariante, C. M., & Arseneault, L. (2014). Why some children with externalising problems develop internalising symptoms: testing two pathways in a genetically sensitive cohort study. *Journal of child psychology and psychiatry*.

Whitmer, A. J., & Gotlib, I. H. (2012). Switching and backward inhibition in major depressive disorder: The role of rumination. *Journal of Abnormal Psychology, 121*(3), 570.

Wickramaratne, P. J., & Weissman, M. M. (1993). Using family studies to understand comorbidity. *European Archives of Psychiatry and Clinical Neuroscience, 243*(3-4), 150-157.

Williams, J. M., Mathews, A., & MacLeod, C. (1996). The emotional Stroop task and psychopathology. *Psychological Bulletin, 120*(1), 3-24.

Williamson, D. E., Birmaher, B., Dahl, R. E., & Ryan, N. D. (2005). Stressful life events in anxious and depressed children. *Journal of Child and Adolescent Psychopharmacology, 15*(4), 571-580.

Willis, T. A., Day, K., Eley, T. C., Chorpita, B. F., & Gregory, A. M. (Unpublished). Adapting the Revised Child Anxiety and Depression Scale for use in longitudinal studies of anxiety across early adulthood: The Revised Symptoms of Anxiety Scale.

Wittchen, H. U., Kessler, R. C., Pfister, H., & Lieb, M. (2000). Why do people with anxiety disorders become depressed? A prospective-longitudinal community study. *Acta Paediatrica Scandinavica, 102*(406), 14-23.

Woodward, L. J., & Fergusson, D. M. (2001). Life course outcomes of young people with anxiety disorders in adolescence. *Journal of the American Academy of Child and Adolescent Psychiatry, 40*(9), 1086-1093.

World Health Organization. (1992). *The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines*: Geneva: World Health Organization.

Wright, K. D., Asmundson, G. J. G., McCreary, D. R., Stewart, S. H., McLaughlin, E., Comeau, M. N., & Walsh, T. M. (2010). Confirmatory Factor Analysis of the Childhood Anxiety Sensitivity Index: A Gender Comparison. *Cognitive Behaviour Therapy, 39*(3), 225-235. doi:10.1080/16506073.2010.486840

Wright, S. (1921). Systems of mating. *Genetics, 6*, 111-178.

Yang, J., Lee, S. H., Goddard, M. E., & Visscher, P. M. (2011). GCTA: a tool for genome-wide complex trait analysis. *The American Journal of Human Genetics, 88*(1), 76-82.

Yang, J., Manolio, T. A., Pasquale, L. R., Boerwinkle, E., Caporaso, N., Cunningham, J. M., . . . Hayes, M. G. (2011). Genome partitioning of genetic variation for complex traits using common SNPs. *Nature Genetics, 43*(6), 519-525.

Yoder, K. A., Longley, S. L., Whitbeck, L. B., & Hoyt, D. R. (2008). A dimensional model of psychopathology among homeless adolescents: Suicidality, internalizing, and externalizing disorders. *Journal of Abnormal Child Psychology, 36*(1), 95-104.

Young, C. C., & Dietrich, M. S. (2015). Stressful Life Events, Worry, and Rumination Predict Depressive and Anxiety Symptoms in Young Adolescents. *Journal of Child and Adolescent Psychiatric Nursing, 28*(1), 35-42.

Young, J. F., Mufson, L., & Davies, M. (2006). Impact of comorbid anxiety in an effectiveness study of interpersonal psychotherapy for depressed adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry, 45*(8), 904-912.

Zaitlen, N., Lindström, S., Pasaniuc, B., Cornelis, M., Genovese, G., Pollack, S., . . . Eyre, S. (2012). Informed conditioning on clinical covariates increases power in case-control association studies. *PLoS Genetics, 8*(11), e1003032.

Zavos, H., Rijsdijk, F. V., Gregory, A. M., & Eley, T. C. (2010). Genetic influences on the cognitive biases associated with anxiety and depression symptoms in adolescents. *Journal of Affective Disorders, 124*(1), 45-53.

Zavos, H., Wong, C., Barclay, N., Keers, R., Mill, J., Rijsdijk, F., . . . Eley, T. (2012). Anxiety sensitivity in adolescence and young adulthood: the role of stressful life events, 5HTTLPR and their interaction. *Depression and anxiety, 29*(5), 400-408.

Zavos, H. M. S., Gregory, A. M., & Eley, T. C. (2012). Longitudinal genetic analysis of anxiety sensitivity. *Developmental Psychology, 48*(1), 204-212. doi:10.1037/a0024996

Zavos, H. M. S., Rijsdijk, F. V., & Eley, T. C. (2012). A Longitudinal, Genetically Informative, Study of Associations Between Anxiety Sensitivity, Anxiety and Depression. *Behavior Genetics, 42*(4), 592-602. doi:10.1007/s10519-012-9535-0

Zeiss, A. M., & Lewinsohn, P. M. (1988). Enduring deficits after remissions of depression: A test of the scar hypothesis. *Behaviour Research and Therapy, 26*(2), 151-158.

Zinbarg, R. E., Brown, T. A., Barlow, D. H., & Rapee, R. M. (2001). Anxiety sensitivity, panic, and depressed mood: a reanalysis teasing apart the contributions of the two levels in the hierarchial structure of the Anxiety Sensitivity Index. *Journal of Abnormal Psychology, 110*(3), 372-377.

Zvolensky, M. J., & Forsyth, J. P. (2002). Anxiety sensitivity dimensions in the prediction of body vigilance and emotional avoidance. *Cognitive Therapy and Research, 26*(4), 449-460.

APPENDIX A - CHAPTER 3 SUPPLEMENTARY MATERIALS

eMethods – Recruitment details

ECHO

Emotions, Cognitions, Heredity and Outcome (ECHO) study is a spin-off from a larger longitudinal sample of twins born in England and Wales during 1994-1996 (TEDS) (Trouton, Spinath, & Plomin, 2002). In order to maximize power and include children with high emotional symptoms, the majority of twins (N=247 pairs) were recruited due to one or both of them scoring within top 15% on child anxiety at age 7, as reported by parents. A smaller group of 'control' pairs were chosen, out of which none of the twins scored high on anxiety symptoms (N=53 pairs). This selection ensured that the data represented a full range of scores on test measures. A total of 11 twin pairs (4%) were excluded because at least one of the twins had co-morbid diagnosis of neurological impairments, autistic spectrum disorders, severe receptive language impairments or persistent attentional difficulties. Zygosity was established using parent-report questionnaires. This method is estimated to be over 95% accurate (Goldsmith, 1991; Price et al., 2000). Where zygosity was ambiguous, DNA was collected from cheek swabs in order to assign zygosity. The social-economic status (SES) of ECHO participants was somewhat higher than a population based sample, where for example 32% of parents were in education until 18 years or more (Meltzer, Gatward, Goodman, & Ford, 2000). The sample characteristics at both waves are presented in the Table 1.

For both waves, parents/guardians provided written informed consent through the post prior to data collection. Data collection was conducted at the Institute of Psychiatry (King's College London, United Kingdom), apart from a small number of children who were visited in their homes. The study was granted ethical approval by the Maudsley Hospital Ethics Committee (London, United Kingdom).

In order to be able to generalize the results from this selected sample to the whole population, a weight was incorporated into all analyses. The weight controls for biases due to ascertainment - oversampling symptomatic children. The weight used the ratio of the selection probability of high symptom families to that of nonsymptomatic families to control for bias associated with ascertainment across waves, and the

inverse of the predicted probability of families remaining at Wave 2 to control for bias associated with attrition. In short, lower weights were assigned to individuals from categories over-represented in the sample, and higher weights to individuals from categories under-represented in the sample relative to the population distribution. The weight did not change the results in a way that would alter the interpretation.

G1219

The G1219 study is a longitudinal study of 3,640 adolescent twins and siblings. The sample was recruited from two sources. First, adolescent offspring of adults from a large-scale population-based study (GENESIS) (Sham et al., 2000) were invited to participate in this or another study (Curran et al., 2003). Of the 3,600 responses, 1,818 adolescents (51%) from 1,294 families agreed to participate in G1219. Second, a random selection of live twin births born between 1985 and 1988 identified by the UK Office of National Statistics were recruited by Heath Authorities and General Practitioners on behalf of G1219 team. Of the 2,947 families contacted, 1,381 (47%) participated. Only respondents aged 12 to 19 were included within the final sample. The present analyses focus on waves 2-4 of the data collection, when the participants were on average 15, 17 and 20 years old. Zygosity was established using parent-report questionnaires assessing the physical similarity between pairs. This method is estimated to be over 95% accurate (Goldsmith, 1991; Price et al., 2000). When there was disagreement between zygosity ratings between wave one and two, DNA was obtained (N=26 pairs) before final classifications were made. The sample characteristics at three waves are presented in the Table 1. Weight was not included in the analyses due to the non-selected nature of the sample. The social-economic status (SES) of G1219 participants was somewhat higher than a population based sample, with 39% educated to A-level or above compared to 32% in the nationally representative sample (Meltzer et al., 2000). Parents from the G1219 sample were also more likely to own their own homes (82% compared to 68%).

For all waves, informed consent was obtained from parents/guardians of all participating adolescents under 16 and from participants themselves when over 16. The study was granted ethical approval by the Research Ethics Committees of the Institute of Psychiatry, South London and Maudsley NHS Trust for all waves, and Goldsmiths, University of London at wave 4.

eTable 1 – Multivariate model fit statistics in adolescence and early adulthood: excluding siblings.

			Comparison to Saturated Model			Comparison to Correlated Factors Solution			Comparison to 2 Factors Independent Pathway Model				
	-2LL	df	χ^2	Δ df	p-value	χ^2	Δ df	p-value	χ^2	Δ df	p-value	AIC	BIC (size-adjusted)
Adolescence (15 years)													
Saturated Model	26715.40	9491										7733.40	28198.25
Correlated Factors Solution	**27125.78**	**9777**	**410.38**	**286**	**<.01**							**7571.78**	**27303.72**
2 Factors Independent Pathway Model	27162.21	9784	446.81	293	<.01	36.43	7	<.01				7594.22	27308.22
1 Factor Independent Pathway Model	27210.27	9787	494.87	296	<.01	84.49	10	<.01	48.06	3	<.01	7636.27	27342.59
Adolescence (17 years)													
Saturated Model	15521.20	5914										3693.20	17004.05
Correlated Factors Solution	**15928.29**	**6200**	**407.09**	**286**	**<.01**							**3528.29**	**16106.23**
2 Factors Independent Pathway Model	15992.47	6207	471.27	293	<.01	64.18	7	<.01				3578.46	16138.47
1 Factor Independent Pathway Model	16010.00	6210	488.80	296	<.01	81.71	10	<.01	17.53	3	<.01	3589.99	16142.31
Young Adulthood (20 years)													
Saturated Model	18182.31	5616										6950.31	19665.16
Correlated Factors Solution	18524.03	5902	341.73	286	.01							6720.03	18701.98
2 Factors Independent Pathway Model	**18537.01**	**5909**	**354.70**	**293**	**.01**	**12.98**	**7**	**0.07**				**6719.01**	**18683.02**
1 Factor Independent Pathway Model	18555.80	5912	373.49	296	<.01	31.77	10	<.01	18.79	3	<.01	6731.80	18688.11

eTable 1 (continued)– Multivariate model fit statistics in adolescence and early adulthood: excluding siblings

Note:

The adolescence sample comes from waves 2-3 and the young adult sample comes from wave 4 from G1219 study. Mean ages provided in the headings.

-*2LL* – minus twice the log likelihood; *df*- degrees of freedom; *Δ df* – degrees of freedom difference; *p* – probability; *AIC* – Akaike's information criterion; *BIC* – Bayesian's information criterion.

The best fitting model (shown in bold) was selected based on the principle of parsimony and lowest AIC and BIC value.

The analyses were repeated excluding siblings in order to establish whether the results hold for narrower age ranges. The exclusion of siblings has not altered the results in a meaningful way, supporting the conclusion that they are applicable to the developmental periods investigated.

eTable 2 – Multivariate genetic analyses at 15 and 17 years, inclusive of physical injury variable

		Descriptive Statistics				Univariate results			Phenotypic correlations with depression		Correlated Factors Solution results			
Wave	N	Mean (SD)	Skew	Kurtosis	α	A	C	E	Full (r_{ph})	Partial	r_A with depression	r_E with depression	Proportion of r_{ph} due to A	Proportion of r_{ph} due to E
Adolescence (15 years)	2628	3.18 (2.47)	.87	3.75	.50	.37 (.25-.44)	.00 (.00-.08)	.63 (.56-.71)	.31 (.28-.39)	-.02 (-.06-.02)	.46 (.35-.58)	.16 (.08-.24)	.69 (.52-.85)	.31 (.15-.48)
Adolescence (17 years)	1590	3.02 (2.51)	.96	3.96	.50	.31 (.07-.40)	.00 (.00-.15)	.69 (.60-.81)	.30 (.26-.34)	.06 (.01-.11)	.23 (.04-.40)	.25 (.15-.35)	.36 (.06-.62)	.64 (.38-.94)

Note

The adolescence sample comes from waves 2-3 from G1219 study. Mean ages provided in the headings.

A – additive genetic influences, *C* – shared environmental influences, *E* – non-shared environmental influences, r_{ph} – phenotypic correlation, r_{ph} – genetic correlation, r_{ph} – non-shared environmental correlation

Descriptive and phenotypic results presented on untransformed variables for comparison with other published samples.

eTable 2 (continued) – Multivariate genetic analyses at 15 and 17 years, inclusive of physical injury variable

95% Confidence Intervals (CIs) are presented in brackets. CIs not inclusive of zeros indicate significant correlations. Non-overlapping CIs mean significant difference between the values.

Partial correlations controlled for all other anxiety variables within time.

The inclusion of the fear of physical injury variable has not altered the fit statistics of the multivariate models in a way that would change the interpretation of results – the correlated factors solution remained the best fitting model at both ages. The fear of physical injury has been modelled as an additional 'fear' variable in the two factors independent pathway model.

C influences were dropped from the multivariate models without a significant deterioration of the fit.

eTable 3 – Univariate results

Trait	Parameter	Childhood (8 years)	Childhood (10 years)	Adolescence (15 years)	Adolescence (17 years)	Young adult (20 years)
Depression	A	.31 (.00-.50)	.00 (.00-.40)	.45 (.26-.57)	.45 (.20-.53)	.40 (.24-.50)
	C	.05 (.00-.33)	.37 (.05-.48)	.06 (.00-.19)	.00 (.00-.19)	.00 (.00-.11)
	E	.65 (.50-.83)	.63 (.48-.75)	.49 (.43-.57)	.55 (.47-.64)	.60 (.50-.70)
Generalized Anxiety	A	.31 (.06-.44)	.27 (.00-.43)	.45 (.25-.52)	.40 (.24-.49)	.36 (.06-.49)
	C	.00 (.00-.17)	.00 (.00-.26)	.00 (.00-.14)	.00 (.00-.10)	.03 (.00-.23)
	E	.69 (.56-.84)	.73 (.57-.91)	.55 (.48-.63)	.60 (.51-.70)	.61 (.51-.74)
Panic	A	.19 (.00-.34)	.14 (.00-.44)	.27 (.06-.45)	.29 (.09-.39)	.32 (.10-.41)
	C	.00 (.00-.20)	.13 (.00-.35)	.10 (.00-.25)	.00 (.00-.13)	.00 (.00-.15)
	E	.81 (.66-.97)	.73 (.56-.90)	.63 (.55-.71)	.71 (.61-.82)	.68 (.59-.79)
Separation Anxiety	A	.28 (.11-.43)	.35 (.02-.50)	.34 (.13-.49)	.41 (.28-.50)	.36 (.21-.45)
	C	.00 (.00-.09)	.00 (.00-.25)	.08 (.00-23)	.00 (.00-.08)	.00 (.00-.10)
	E	.72 (.57-.87)	.65 (.50-.81)	.58 (.51-.66)	.60 (.51-.69)	.64 (.55-.75)
Social Anxiety	A	.05 (.00-.22)	.39 (.00-.53)	.43 (.30-.50)	.28 (.00-.45)	.44 (.16-.54)
	C	.00 (.00-.11)	.00 (.00-.29)	.00 (.00-.08)	.08 (.00-.28)	.01 (.00-.21)
	E	.95 (.83-1.00)	.61 (.47-.78)	.57 (.50-.65)	.65 (.55-.76)	.55 (.46-.66)

eTable 3 – Univariate results (continued)

Note:

The childhood sample comes from ECHO study, the adolescence sample comes from waves 2-3 and the young adult sample comes from wave 4 from G1219 study. Mean ages provided in the headings.

A – additive genetic influences, *C* – shared environmental influences, *E* – non-shared environmental influences

95% Confidence Intervals are presented in brackets. CIs not inclusive of zeros indicate significant correlations. Non-overlapping CIs mean significant difference between the values. The difference in CIs width between the ECHO and G1219 time points reflects larger sample size of G1219 which results in greater power to estimate the parameters precisely.

The ECHO sample was too small to examine sex differences so these were only examined in G1219. Quantitative sex differences imply that genetic and environmental influences differ in magnitude across sex whilst scalar sex differences indicate variance differences between males and females. Scalar sex differences were evident for all variables apart from social concerns at times 3-5, suggesting that males and females showed different variance on most measures. To account for these differences, a scalar was fitted in all twin modeling analyses at these time points.

Depression at time 2 in child sample (ECHO) showed different pattern of parameter estimates than other variables, being influenced by moderate shared environmental factors with no genetic influence. This is due to a low power to distinguish between A and C in the ECHO sample.

eTable 4 – Longitudinal phenotypic continuity of anxiety subscales, within and across anxiety measures.

	Age 15 – Age 17 (Within SCAS)	Age 15- Age 20 (SCAS to RCADS)	Age 17- Age 20 (SCAS to RCADS)
Generalized Anxiety	.47 (.43-.51)	.36 (.32-.40)	.53 (.49-.56)
Panic	.43 (.39-.47)	.39 (.35-.43)	.48 (.44-.52)
Separation Anxiety	.36 (.32-.40)	.39 (.35-.43)	.35 (.31-.39)
Social Phobia	.53 (.49-.56)	.46 (.42-.50)	.58 (.54-.62)

Note:

The adolescence sample comes from waves 2-3 and the young adult sample comes from wave 4 from G1219 study. Mean ages provided in the headings.

SCAS - Spence Children's Anxiety Scale (Spence, 1998); *RCADS* - Revised Child Anxiety and Depression Scale (Chorpita, Yim, Moffitt, Umemoto, & Francis, 2000).

95% Confidence Intervals (CIs) are presented in brackets. CIs not inclusive of zeros indicate significant correlations. Non-overlapping CIs mean significant difference between the values.

The analyses (Pearson's correlations) were conducted in order to check for measurement effects, and the results suggest a comparable continuity of the scores within and across anxiety measures.

eTable 5 – Multivariate model fit statistics in adolescence and early adulthood. Submodel comparisons to drop C and A.

			Comparison to Saturated Model			AIC	BIC (size-adjusted)
	-2LL	df	X^2	Δ df	p-value		
Adolescence (15 years)							
Correlated Factors Solution – ACE model	35203.32	12649				9905.32	35470.98
Correlated Factors Solution – AE model	**35207.38**	**12664**	**4.06**	**15**	**1.00**	**9879.38**	**35400.69**
Correlated Factors Solution – CE model	35262.08	12664	58.76	15	<.01	9934.08	35455.39
Adolescence (17 years)							
Correlated Factors Solution – ACE model	19754.74	7668				4418.74	20022.40
Correlated Factors Solution – AE model	**19758.02**	**7683**	**3.28**	**15**	**1.00**	**4392.02**	**19951.33**
Correlated Factors Solution – CE model	19813.65	7683	58.91	15	<.01	4447.65	20006.96
Young Adulthood (20 years)							
2 Factor Independent Pathway Model – ACE model	23559.32	7543				8473.32	23767.51
2 Factors Independent Pathway Model – AE model	**23566.13**	**7553**	**6.81**	**10**	**.74**	**8460.13**	**23724.74**
2 Factor Independent Pathway Model –CE model	23619.75	7556	60.43	13	<.01	8507.74	23763.49

eTable 5 (continued) – Multivariate model fit statistics in adolescence and early adulthood. Submodel comparisons to drop C and A.

Note:

The adolescence sample comes from waves 2-3 and the young adult sample comes from wave 4 from the G1219 study. Mean ages provided in the headings.

-2LL – minus twice the log likelihood; *df*- degrees of freedom; *Δ df* – degrees of freedom difference; *p* – probability; *AIC* – Akaike's information criterion.

The best fitting model (shown in bold) was selected based on the principle of parsimony and lowest AIC and BIC value. Shared-environmental, but not genetic influences can be dropped from the models without significant deterioration of the fit. The AIC values suggest that dropping C lead to improvement of the model fit at these three waves.

APPENDIX B - CHAPTER 4 SUPPLEMENTARY MATERIALS

Table B1 – Longitudinal Cholesky results with confidence intervals

Path	Depression	Panic	Generalized Anxiety	Separation Anxiety	Social Phobia
$a1_1$	.52 (.46-.58)	.40 (.33-.46)	.45 (.38-.51)	.44 (.37-.50)	.42 (.35-.49)
$a1_2$	.29 (.21-.37)	.17 (.09-.26)	.21 (.13-.31)	.14 (.08-.22)	.23 (.15-.32)
$a1_3$	.26 (.17-.35)	.20 (.12-.30)	.18 (.11-.27)	.12 (.06-.20)	.27 (.18-.37)
$a2_2$	.18 (.09-.26)	.25 (.15-.35)	.18 (.08-.28)	.27 (.16-.36)	.15 (.07-.23)
$a2_3$	.01 (.00-.06)	.08 (.01-.17)	.10 (.02-.21)	.01 (.00-.06)	.08 (.01-.18)
$a3_3$	.13 (.03-.22)	.07 (.00-.16)	.11 (.01-.20)	.23 (.13-.32)	.09 (.00-.17)
$e1_1$	.48 (.42-.54)	.60 (.54-.67)	.55 (.49-.62)	.56 (.50-.63)	.58 (.51-.65)
$e1_2$	.02 (.01-.05)	.03 (.01-.07)	.05 (.02-.09)	.01 (.00-.03)	.08 (.04-.12)
$e1_3$	.00 (.00-.02)	.01 (.00-.03)	.00 (.00-.02)	.03 (.01-.06)	.02 (.00-.04)
$e2_2$	.51 (.44-.59)	.54 (.46-.64)	.56 (.47-.65)	.59 (.50-.68)	.54 (.47-.62)
$e2_3$	.06 (.03-.10)	.03 (.00-.07)	.05 (.02-.10)	.01 (.00-.03)	.06 (.03-.10)
$e3_3$	.55 (.47-.64)	.61 (.53-.70)	.56 (.48-.65)	.61 (.52-.71)	.49 (.42-.57)

Table B1 (continued) – Longitudinal Cholesky results with confidence intervals

Notes:

a1$_{1\text{-}3}$ and *e1*$_{1\text{-}3}$ – proportion of total variance accounted for by the genetic/environmental factor (A1/E1) that emerged at time 1 (age 15) on the variables at each time point (ages 15, 17 and 20) (specific time point denoted by subscript).

a2$_{2\text{-}3}$ and *e2*$_{2\text{-}3}$ – proportion of total variance accounted for by the genetic/environmental factor (A2/E2) that emerged at time 2 (age 17) on the variables at time points 2 (age 17) and 3 (age 20) (specific time point denoted by subscript).

a3$_3$ and *e3*$_3$ – proportion of total variance accounted for by the genetic/environmental factor (A3/E3) that emerged at time 3 (age 20) on the variables at time 3 (age 20).

All paths are squared. Square root of these values should be taken to obtain variance paths.

95% Confidence Intervals (CIs) are presented in brackets. CIs not inclusive of zeros indicate significant correlations. Non-overlapping CIs mean significant difference between the values.

AE models are presented, as C influences were not significant and were dropped from the multivariate models without a significant deterioration of the fit (Table B2). The AIC values suggest that dropping C lead to improvement of the model fit at these three waves. Full ACE results are presented in Tables B3-5 for completeness.

Univariate results have been presented before (Chapter 3), but can also be calculated by adding all the paths contributing to the variable (e.g. heritability of depression at time 3 is $a1_3$+ $a2_3$+ $a3_3$=.40

Table B2 - Model fit statistics for longitudinal Cholesky decompositions and Common pathway model

	Comparison to Saturated Model					Comparison to Cholesky decomposition (ACE)				
	-2LL	df	χ^2	Δ df	p-value	χ^2	Δ df	p-value	AIC	BIC (size-adjusted)
Depression										
Saturated model	9584.49	5408							-1231.51	10655.14
Cholesky decomposition (ACE)	9923.09	5600	338.60	192	<.05				-1276.91	10042.05
Cholesky decomposition (AE)	**9925.37**	**5606**	**340.88**	**198**	**<.05**	**2.28**	**6**	**.89**	**-1286.63**	**10014.59**
Cholesky decomposition (CE)	9971.37	5606	386.88	198	<.05	48.28	6	<.05	-1240.63	10060.59
Cholesky decomposition (E)	10196.61	5612	612.12	204	<.05	273.52	12	<.05	-1027.39	10256.09
Panic										
Saturated model	11382.69	5375							632.69	10897.22
Cholesky decomposition (ACE)	11653.70	5567	271.01	192	<.05				519.70	11772.66
Cholesky decomposition (AE)	**11656.51**	**5573**	**273.82**	**198**	**<.05**	**2.80**	**6**	**.83**	**510.51**	**11745.73**
Cholesky decomposition (CE)	11687.32	5573	304.63	198	<.05	33.62	6	<.05	541.32	11776.54
Cholesky decomposition (E)	11833.37	5579	450.68	204	<.05	179.67	12	<.05	675.37	11892.85
Generalized Anxiety										
Saturated model	26527.66	5379							15769.66	27598.31
Cholesky decomposition (ACE)	26785.26	5571	257.60	192	<.05				15643.26	26904.22
Cholesky decomposition (AE)	**26786.55**	**5577**	**285.89**	**198**	**<.05**	**1.29**	**6**	**.97**	**15632.55**	**26875.77**
Cholesky decomposition (CE)	26818.16	5577	290.51	198	<.05	32.90	6	<.05	15664.16	26907.38
Cholesky decomposition (E)	26970.31	5583	442.65	204	<.05	185.05	12	<.05	15804.31	27029.79
Separation Anxiety										
Saturated model	7599.95	5381							-3162.05	8670.60
Cholesky decomposition (ACE)	7886.44	5573	286.49	192	<.05				-3259.56	8005.41
Cholesky decomposition (AE)	**7890.10**	**5579**	**290.14**	**198**	**<.05**	**3.65**	**6**	**.72**	**-3267.91**	**7979.32**
Cholesky decomposition (CE)	7923.74	5579	323.78	198	<.05	37.30	6	<.05	-3234.26	8012.96
Cholesky decomposition (E)	8095.58	5585	495.63	204	<.05	209.14	12	<.05	-3074.42	8155.06
Social Anxiety										
Saturated model	28449.24	5387							17675.24	29519.89
Cholesky decomposition (ACE)	28693.82	5582	244.58	192	<.05				17529.82	28797.91
Cholesky decomposition (AE)	**28694.79**	**5588**	**245.55**	**198**	**<.05**	**0.96**	**6**	**.99**	**17518.79**	**28769.14**
Cholesky decomposition (CE)	28727.05	5588	277.81	198	<.05	33.22	6	<.05	17551.05	28801.40
Cholesky decomposition (E)	28872.23	5594	422.99	204	<.05	178.40	12	<.05	17684.23	28916.84
All variables										
Saturated model	73044.58	25535							21974.58	84758.52
Common pathway model (ACE)	76373.36	27793	3328.78	2258	<.05				20787.36	77473.75
Common pathway model (AE)	**76381.08**	**27853**	3336.50	2318	**<.05**	**7.72**	**60**	**1.00**	**20675.08**	**77184.07**
Common pathway model (CE)	76498.78	27853	3454.20	2318	<.05	125.42	60	<.05	20792.78	77301.77
Common pathway model (E)	77138.64	27913	4094.06	2378	<.05	765.28	120	<.05	21312.64	77644.22

Table B2 (continued) - Model fit statistics for longitudinal Cholesky decompositions and Common pathway model

Notes:

-2LL – minus twice the log likelihood; *df*- degrees of freedom; *Δ df* – degrees of freedom difference; *p* – probability; *AIC* – Akaike's information criterion; *BIC* – Bayesian's information criterion.

The best fitting model (shown in bold) was selected based on the principle of parsimony and lowest AIC and BIC value. A difference in AIC between two models of 2 or less, provides equivalent support for both models (in which case the most parsimonious model should be chosen), a difference of 3 indicates that the lower AIC model has considerably more support and a difference of more than 10, indicates that the lower AIC model is a substantially better fit compared to the higher AIC model (Wagenmakers & Farrell, 2004). Shared-environmental, but not genetic influences can be dropped from the models without significant deterioration of the fit. The AIC and BIC values suggest that dropping C lead to improvement of the model fit at these three waves.

The Cholesky decompositions and common pathway model were significantly different from the corresponding saturated models, indicating poor fit, however this is common in studies with large sample sizes because minimal variance differences between groups can be highly statistically significant.

Quantitative sex differences imply that genetic and environmental influences differ in magnitude across sex whilst scalar sex differences indicate variance differences between males and females. Scalar sex differences were evident for all variables apart from social concerns at times 1-3, suggesting that males and females showed different variance on most measures. To account for these differences, a scalar was fitted in all twin modeling analyses at these time points.

Table B3 – Longitudinal Cholesky results with confidence intervals (full ACE model)

Path	Depression	Panic	Generalized Anxiety	Separation Anxiety	Social Phobia
$a1_1$	.45 (.29-.56)	.30 (.13-.44)	.41 (.23-.51)	.28 (.12-.45)	.42 (.29-.49)
$a1_2$	.38 (.19-.50)	.17 (.05-.38)	.21 (.08-.38)	.22 (.05-.44)	.23 (.09-.37)
$a1_3$	.34 (.18-.45)	.31 (.11-.43)	.26 (.07-.43)	.26 (.06-.42)	.27 (.13-.42)
$a2_2$	.08 (.00-.24)	.24 (.05-.35)	.18 (.02-.27)	.19 (.00-.42)	.11 (.00-.22)
$a2_3$	.05 (.00-.19)	.04 (.01-.16)	.06 (.00-.24)	.01 (.00-.03)	.16 (.00-.26)
$a3_3$	.00 (.00-.20)	.00 (.00-.13)	.00 (.00-.18)	.07 (.00-.29)	.00 (.00-.16)
$c1_1$	.06 (.00-.18)	.08 (.00-.21)	.03 (.00-.16)	.12 (.00-.24)	.00 (.00-.09)
$c1_2$	.01 (.00-.14)	.01 (.00-.09)	.00 (.00-.10)	.00 (.00-.06)	.04 (.00-.18)
$c1_3$	.00 (.00-.09)	.00 (.00-.10)	.04 (.00-.18)	.01 (.00-.09)	.01 (.00-.16)
$c2_2$	.00 (.00-.14)	.00 (.37-.05)	.00 (.00-.06)	.00 (.00-.09)	.00 (.00-.13)
$c2_3$	.00 (.00-.09)	.00 (.00-.11)	.00 (.00-.17)	.00 (.00-.11)	.00 (.00-.13)
$c3_3$	.00 (.00-.07)	.00 (.00-.10)	.00 (.00-.13)	.00 (.00-.11)	.00 (.00-.11)
$e1_1$	.49 (.43-.56)	.62 (.55-.70)	.56 (.49-.64)	.60 (.52-.67)	.58 (.51-.65)
$e1_2$	.02 (.01-.05)	.04 (.01-.07)	.05 (.02-.09)	.01 (.00-.03)	.07 (.04-.12)
$e1_3$	.00 (.00-.01)	.01 (.00-.03)	.00 (.00-.02)	.02 (.01-.06)	.02 (.00-.04)
$e2_2$	.52 (.44-.59)	.54 (.46-.64)	.56 (.47-.65)	.59 (.50-.68)	.55 (.47-.63)
$e2_3$	.06 (.02-.11)	.03 (.00-.07)	.05 (.02-.10)	.01 (.00-.03)	.05 (.03-.10)
$e3_3$	.55 (.47-.63)	.61 (.53-.69)	.58 (.49-.66)	.62 (.53-.72)	.50 (.42-.57)

Table B3 (Continued) – Longitudinal Cholesky results with confidence intervals (full ACE model)

Notes:

a1$_{1\text{-}3}$, *c1*$_{1\text{-}3}$ and *e1*$_{1\text{-}3}$ – proportion of total variance accounted for by the genetic/shared environmental/ non-shared environmental factor (A1/C1/E1) that emerged at time 1 (age 15) on the variables at each time point (ages 15, 17 and 20) (specific time point denoted by subscript).

a2$_{2\text{-}3}$, *c2*$_{2\text{-}3}$ and *e2*$_{2\text{-}3}$ – proportion of total variance accounted for by the genetic/shared environmental/ non-shared environmental factor (A2/C2/E2) that emerged at time 2 (age 17) on the variables at time points 2 (age 17) and 3 (age 20) (specific time point denoted by subscript).

a3$_3$, *c3*$_3$ and *e3*$_3$ – proportion of total variance accounted for by the genetic/shared environmental/ non-shared environmental factor (A3/C3/E3) that emerged at time 3 (age 20) on the variables at time 3 (age 20).

All paths are squared. Square root of these values should be taken to obtain variance paths.

95% Confidence Intervals (CIs) are presented in brackets. CIs not inclusive of zeros indicate significant correlations. Non-overlapping CIs mean significant difference between the values.

Univariate results have been presented before (Chapter 3), but can also be calculated by adding all the paths contributing to the variable (e.g. heritability of depression at time 3 is a1$_3$+ a2$_3$+ a3$_3$=.39).

Table B4– Common pathway model results (full ACE model): Genetic and environmental influences on the latent factor, and latent factor and time-specific influences on each variable.

		Depression			Panic			Generalized Anxiety			Separation Anxiety			Social Anxiety		
Etiological influences on the latent factor	A_l	.76 (.54-.84)			.66 (.42-.77)			.63 (.36-.74)			.69 (.40-.83)			.60 (.33-.71)		
	C_l	.00 (.00-.16)			.00 (.00-.17)			.00 (.00-.19)			.01 (.00-.21)			.01 (.00-.21)		
	E_l	.24 (.16-.35)			.34 (.23-.46)			.37 (.26-.49)			.31 (.17-.46)			.39 (.29-.51)		
Mean age		15	17	20	15	17	20	15	17	20	15	17	20	15	17	20
Latent factor influences on each variable	L	.63 (.59-.67)	.78 (.73-.82)	.58 (.53-.62)	.56 (.52-.60)	.71 (.66-.76)	.62 (.57-.66)	.57 (.53-.61)	.82 (.78-86)	.58 (.53-.63)	.55 (.51-.60)	.46 (.39-.52)	.60 (.55-.66)	.62 (.58-.65)	.82 (.78-.86)	.68 (.64-.72)
Time-specific etiological influences on each variable	A_s	.11 (.00-.25)	.02 (.00-.10)	.13 (.00-.22)	.10 (.00-.22)	.11 (.02-.20)	.05 (.00-.14)	.21 (.05-.29)	.02 (.00-.08)	.07 (.00-.19)	.10 (.00-.25)	.24 (.08-.35)	.10 (.00-.20)	.15 (.04-.23)	.02 (.00-.06)	.09 (.00-.17)
	C_s	.07 (.00-.16)	.02 (.00-.07)	.00 (.00-.10)	.06 (.00-.15)	.01 (.00-.06)	.02 (.00-.10)	.01 (.00-.12)	.00 (.00-.03)	.04 (.00-.14)	.08 (.00-.18)	.01 (.00-.11)	.00 (.00-.11)	.01 (.00-.09)	.00 (.00-.04)	.00 (.00-.11)
	E_s	.43 (.36-.49)	.35 (.28-.42)	.53 (.45-.63)	.53 (.46-.60)	.38 (.29-.46)	.56 (.47-.64)	.46 (.39-.53)	.31 (.23-.38)	.55 (.46-.64)	.51 (.43-.58)	.54 (.45-.64)	.53 (.44-.63)	.46 (.39-.53)	.30 (.24-.37)	.44 (.37-.53)

Table B4 (continued)– Common pathway model results (full ACE model): Genetic and environmental influences on the latent factor, and latent factor and time-specific influences on each variable.

Notes:

A - additive genetic effects; C – shared environmental effects; E - non-shared environmental effects; L – Latent factor.

Mean ages provided in the headings.

95% Confidence Intervals (CIs) are presented in brackets. CIs not inclusive of zeros indicate significant influences. Non-overlapping CIs mean significant difference between the values.

L needs to be squared to inform about the proportion of total variance accounted for by the latent factor. L^2 should be multiplied by A_l/ C_l /E_l to obtain the proportion of the total variance due to the genetic/shared environmental/non-shared environmental influences from the latent factor, respectively. Total variance of a trait = $L^2 + A_s + C_s + E_s$

Table B5– Common pathway model results (full ACE model): Phenotypic, genetic and environmental correlations between the latent factors and time-specific influences at 15, 17 and 20 years

		Depression	Panic	Generalized Anxiety	Separation Anxiety
Latent Factors					
Panic	r_{phl}	.72 (.66-.80)			
	r_{Al}	.75 (.64-.92)			
	r_{Cl}	1.00 (-.58-1.00)			
	r_{El}	.66 (.44-.85)			
Generalized Anxiety	r_{phl}	.74 (.68-.80)	.83 (.78-.89)		
	r_{Al}	.81 (.70-.94)	.87 (.77-.99)		
	r_{Cl}	1.00 (-1.00-1.00)	1.00 (-1.00-1.00)		
	r_{El}	.60 (.41-.76)	.75 (.60-.88)		
Separation Anxiety	r_{phl}	.58 (.50-.69)	.76 (.69-.82)	.80 (.74-.88)	
	r_{Al}	.60 (.44-.81)	.78 (.63-.90)	.86 (.74-1.00)	
	r_{Cl}	1.00 (-.89-1.00)	1.00 (-1.00-1.00)	1.00 (-1.00-1.00)	
	r_{El}	.55 (.27-.80)	.73 (.50-.95)	.69 (.49-.88)	
Social Anxiety	r_{phl}	.63 (.56-.71)	.62 (.54-.69)	.75 (.69-.81)	.64 (.56-.71)
	r_{Al}	.68 (.54-.86)	.68 (.49-.83)	.77 (.62-.91)	.75 (.58-.92)
	r_{Cl}	1.00 (-1.00-1.00)	1.00 (-1.00-1.00)	1.00 (-1.00-1.00)	1.00 (-1.00-1.00)
	r_{El}	.56 (.37-.73)	.52 (.34-.68)	.71 (.57-.83)	.46 (.24-.66)
Time-specific influences at 15					
Panic	r_{phs}	.41 (.29-.49)			
	r_{As}	.96 (-1.00-1.00)			
	r_{Cs}	.58 (68-1.00)			
	r_{Es}	.30 (.21-.39)			
Generalized Anxiety	r_{phs}	.44 (.33-.52)	.47 (.38-.54)		
	r_{As}	.64 (-.75-1.00)	.52 (-1.00-1.00)		
	r_{Cs}	.58 (-1.00-1.00)	1.00(-1.00-1.00)		
	r_{Es}	.38 (.28-.46)	.47 (.38-.54)		
Separation Anxiety	r_{phs}	.31 (.19-.43)	.34 (.24-.44)	.41 (.31-.51)	
	r_{As}	.22 (-1.00-1.00)	.30 (-1.00-1.00)	.58 (-1.00-1.00)	
	r_{Cs}	.57 (-1.00-1.00)	1.00(-1.00-1.00)	1.00(-1.00-1.00)	
	r_{Es}	.33 (.23-.42)	.28 (.19-.37)	.37 (.27-.46)	
Social Anxiety	r_{phs}	.34 (.24-.42)	.35 (.25-.42)	.48 (.40-.53)	.45 (.36-.53)
	r_{As}	.59 (-.94-1.00)	.63 (-1.00-1.00)	.80 (.41-.99)	.69 (-1.00-1.00)
	r_{Cs}	.88 (-1.00-1.00)	.90 (-1.00-1.00)	.90 (-1.00-1.00)	.90 (-1.00-1.00)
	r_{Es}	.27 (.17-.37)	.28 (.18-.37)	.35 (.26-.44)	.39 (.30-.48)
Time-specific influences at 17					
Panic	r_{phs}	.22 (.10-.32)			
	r_{As}	.82 (.42-1.00)			
	r_{Cs}	-1.00(-1.00-1.00)			
	r_{Es}	.15 (.01-.28)			
Generalized Anxiety	r_{phs}	.28 (.16-.39)	.39 (.29-.49)		
	r_{As}	.46 (-1.00-1.00)	.42 (-1.00-1.00)		
	r_{Cs}	1.00 (-1.00-1.00)	-.99(-1.00-1.00)		
	r_{Es}	.27 (.13-.40)	.40 (.25-.52)		
Separation Anxiety	r_{phs}	-.09 (-.20--.01)	.00 (-.10-.09)	.11 (.01-.21)	
	r_{As}	-.15 (-1.00-.97)	-.26 (-1.00-.16)	.03 (-1.00-1.00)	
	r_{Cs}	-1.00(-1.00-1.00)	1.00(-1.00-1.00)	-1.00(-1.00-1.00)	
	r_{Es}	-.09 (-.22-.04)	.10 (-.04-.23)	.14 (.00-.27)	

Social Anxiety	r_{phs}	.10 (-.01-.22)	.06 (-.06-.17)	.16 (.04-.28)	.05 (-.05-.14)
	r_{As}	-.80 (-1.00-1.00)	-.84 (-1.00-.11)	-.64 (-1.00-1.00)	.56 (-.25-1.00)
	r_{Cs}	1.00 (-1.00-1.00)	-.99(-1.00-1.00)	1.00(-1.00-1.00)	-1.00 (-1.00-1.00)
	r_{Es}	.17 (.03-.29)	.20 (.06-.32)	.22 (.06-.35)	-.05 (-.18-.08)
Time-specific influences at 20					
Panic	r_{phs}	.36 (.26-.43)			
	r_{As}	.74 (-1.00-1.00)			
	r_{Cs}	.88 (.66-1.00)			
	r_{Es}	.31 (.20-.41)			
Generalized Anxiety	r_{phs}	.44 (.33-.51)	.48 (.37-.54)		
	r_{As}	.63 (-1.00-1.00)	.92 (-1.00-1.00)		
	r_{Cs}	-.20 (-1.00-1.00)	-.44 (-1.00-1.00)		
	r_{Es}	.41 (.31-.50)	.44 (.35-.52)		
Separation Anxiety	r_{phs}	.39 (.29-.46)	.46 (.36-.53)	.46 (.36-.54)	
	r_{As}	.71 (-.91-1.00)	.87 (-1.00-1.00)	.60 (-1.00-1.00)	
	r_{Cs}	-30 (-1.00-1.00)	-.48 (-1.00-1.00)	.99 (-1.00-1.00)	
	r_{Es}	.32 (.21-.42)	.41 (.32-.51)	.44 (.35-.53)	
Social Anxiety	r_{phs}	.45 (.40-.50)	.46 (.37-.54)	.58 (.48-.64)	.43 (.33-.53)
	r_{As}	.73 (-1.00-1.00)	.74 (-1.00-1.00)	.90 (-1.00-1.00)	.37 (-1.00-1.00)
	r_{Cs}	.99 (-.12-1.00)	.83 (-1.00-1.00)	-.14 (-1.00-1.00)	-.24 (-1.00-1.00)
	r_{Es}	.39 (.28-.48)	.43 (.34-.53)	.53 (.45-.62)	.45 (.34-.55)

Notes:

r_{phl} - Phenotypic correlations between the latent factors; r_{Al} - Genetic correlations between the latent factors; r_{Cl} – Shared environmental correlations between the latent factors; r_{El} – Non-shared environmental correlations between the latent factors; r_{phs} - Phenotypic correlations between the time-specific influences; r_{As} - Genetic correlations between the time-specific influences; r_{Cs} – Shared environmental correlations between the time-specific influences; r_{Es} – Non-shared environmental correlations between the time-specific influences.

95% Confidence Intervals (CIs) are presented in brackets. CIs not inclusive of zeros indicate significant correlations. Non-overlapping CIs mean significant difference between the values.

APPENDIX C - CHAPTER 5 SUPPLEMENTARY MATERIALS

Table S1. Univariate genetic, shared environment and non-shared environmental estimates for anxiety sensitivity subscales, anxiety and depression in childhood, adolescence and early adulthood.

		Parameter Estimates		
	Wave	**A**	**C**	**E**
AS Physical	1	.33 (.12-.48)	.00 (.00-.13)	.67 (.52-.83)
	2	.34 (.00-.48)	.00 (.00-.32)	.66 (.52-.84)
	3	.35 (.16-.45)	.04 (.00-.17)	.61 (.54-.69)
	4	.22 (.05-.40)	.12 (.00-.25)	.66 (.57-.65)
	5	.29 (.05 - .43)	.04 (.00 - .20)	.68 (.57 - .79)
AS Social	1	.15 (.00-.31)	.00 (.00-.17)	.85 (.69-1.00)
	2	.22 (.00-.40)	.00 (.00-.14)	.78 (.60-.98)
	3	.25 (.09-.34)	.02 (.00-.13)	.73 (.66-.81)
	4	.23 (.07-.42)	.04 (.00-.15)	.74 (.64-.84)
	5	.24 (.09 - .34)	.00 (.00 - .10)	.76 (.66 - .86)
AS Mental	1	.33 (.15-.48)	.00 (.00-.09)	.67 (.52-.83)
	2	.36 (.11-.52)	.00 (.00-.16)	.64 (.48-.82)
	3	.39 (.22-.47)	.00 (.00-.12)	.61 (.53-.69)
	4	.25 (.07-.42)	.06 (.00-.17)	.69 (.57-.80)
	5	.30 (.13 - .43)	.02 (.00 - .13)	.68 (.57 - .80)
Anxiety	1	.27 (.04-.41)	.00 (.00-.17)	.73 (.59-.87)
	2	.31 (.00-.53)	.08 (.00-.39)	.61 (.47-.79)
	3	.46 (.29-.57)	.05 (.00-.18)	.49 (.43-.56)
	4	.40 (.25-.51)	.02 (.00-.12)	.59 (.49-.68)
	5	.41 (.20 - .55)	.05 (.00 - .20)	.54 (.45 - .64)
Depression	1	.31 (.00-.51)	.05 (.00-.33)	.64 (.49-.82)
	2	.00 (.00-.37)	.31 (.01-.43)	.69 (.55-.81)
	3	.39 (.10-.54)	.10 (.00-.23)	.51 (.45-.59)
	4	.38 (.17-.53)	.06 (.00-.21)	.55 (.46-.65)
	5	.34 (.16 - .48)	.05 (.00- .17)	.61 (.51 - .71)

Notes

A-Additive Genetic Parameters, *C* – Shared Environmental Parameters, *E* – Non-shared Environmental Parameters, *AS* – Anxiety Sensitivity.

95% Confidence Intervals (CIs) are presented in brackets. CIs not including 0 indicate significant estimates. Non-overlapping CIs mean significant difference between the values.

Waves 1-2 come from the ECHO sample when participants had mean ages of 8 and 10 years, respectively. Waves 3-5 come from the G1919 sample. Mean ages were 15, 17 and 20 years, respectively. The difference in the range of CIs between the ECHO and G1219 waves reflects larger sample size of G1219 which results in greater power to estimate parameters precisely.

Depression at wave 2 in the child sample (ECHO) showed a different pattern of parameter estimates than at other time points, being influenced by moderate shared environmental factors with no genetic influence. This is due to a low power to distinguish between A and C in the ECHO sample. For this reason, genetic and environmental associations between depression and the other constructs at this wave are not discussed.

Table S2. Model fitting statistics for multivariate genetic analyses

	-2LL	*df*	χ^2	Δ *df*	*p*	AIC
Wave 1						
Saturated	7329.86	2747				1835.86
Correlated Factors Solution	7433.76	2827	103.91	80	.04	1779.76
Wave 2						
Saturated	5559.60	2058				1443.60
Correlated Factors Solution	5665.53	2138	105.93	80	.03	1389.53
Wave 3						
Saturated	31129.98	12216				6697.98
Correlated Factors Solution	31896.00	12680	766.02	464	.00	6536.00
Wave 4						
Saturated	18161.86	7270				3621.86
Correlated Factors Solution	18972.69	7734	810.83	464	.00	3504.69
Wave 5						
Saturated	17612.20	6823				3966.20
Correlated Factors Solution	18196.85	7283	584.66	464	.00	3630.85

Notes:

-2LL – minus twice the log likelihood; *AIC* – Akaike's information criterion; *p* – probability, *df*- degrees of freedom

Table S2 (continued). Model fitting statistics for multivariate genetic analyses

Model fit to a saturated model was assessed at each wave using minus twice the log likelihood (−2ll) of the observations and Akaike's information criterion (AIC). When two models are nested (i.e. one is a more constrained version of the other) then the differences in −2ll can be used to select the best fitting model since it is distributed as chi-square. A significant increase in chi-square of the reduced model suggests the model is a worse fit of the data than the full model. However, this is only a relative measure of fit and chi-square distribution does not vary linearly with change in df and models with large df are harder to fit. Instead, AIC was used to compare both fit and parsimony. Lower, negative values indicate better fit.

Table S3. Shared environmental correlations between anxiety sensitivity dimensions and anxiety and depression across childhood, adolescence and early adulthood

		Anxiety Sensitivity		
		Physical	Social	Mental
Wave 1	Anxiety	-.11	-.93	.74
Child		(-1.00 – 1.00)	(-1.00 – 1.00)	(-1.00 – 1.00)
(mean age 8)	Depression	.15	.43	.48
		(-1.00 – 1.00)	(-1.00 – 1.00)	(-1.00 – 1.00)
Wave 2	Anxiety	-.01	-.18	.02
Child		(-1.00 – 1.00)	(-1.00 – 1.00)	(-1.00 – 1.00)
(mean age 10)	Depression	.19	-.26	.04
		(-1.00 – 1.00)	(-1.00 – 1.00)	(-1.00 – 1.00)
Wave 3	Anxiety	.99	.17	.41
Adolescent		(-1.00 – 1.00)	(-1.00 – 1.00)	(-1.00 – 1.00)
(mean age 15)	Depression	.57	.95	.50
		(-1.00 - .1.00)	(-1.00 – 1.00)	(-1.00 – 1.00)
Wave 4	Anxiety	.99	.97	.98
Adolescent		(-1.00 – 1.00)	(-1.00 – 1.00)	(-1.00 – 1.00)
(mean age 17)	Depression	.78	.97	.95
		(-1.00 – 1.00)	(-1.00 – 1.00)	(-1.00 – 1.00)
Wave 5	Anxiety	.42	.79	-.62
Adult		(-.59 – 1.00)	(-1.00 – 1.00)	(-1.00 – 1.00)
(mean age 20)	Depression	-.18	.28	1.00
		(-1.00 – 1.00)	(-1.00 – 1.00)	(-1.00 – 1.00)

Notes:

95% Confidence Intervals are presented in brackets. CIs not inclusive of zeros indicate significant correlations. Owing to small, non-significant shared environmental influences on all variables, shared environmental correlations also have wide confidence intervals, the majority spanning from -1.00 to 1.00 and thus it is not meaningful to interpret these associations.

APPENDIX D - CHAPTER 6 SUPPLEMENTARY MATERIALS

Table A1 – Descriptive statistics, cross twin correlations and univariate results separately for males and females.

	Descriptive Statistics (males/females)			Cross twin correlations (males/females)		Univariate influences (males/females)		
	N (Individuals)	*Mean (SD), range*	*Skew*	r_{MZ}	r_{DZ}	A	C	E
Mindfulness	837/1,281	8.58 (4.30), 0-21/ 9.21 (4.39), 0-23	-.02/-.09	.42 (.34-.49)/ .33 (.25-.41)	.13 (.06-.20)/ .16 (.09-.23)	.33 (.08-.48)/ .32 (.08-.42)	.04 (.00-.23)/ .01 (.00-.21)	.63 (.51-.76)/ .67 (.58-.76)
Depression	4,264/5,345	2.63 (3.46), 0-26/ 4.41 (4.91), 0-26	2.28/1.68	.34 (.30-.38)/ .41 (.38-.44)	.18 (.15-.22)/ .25 (.22-.28)	.30 (.12-.40)/ .15 (.06-.27)	.08 (.02-.22)/ .27 (.17-.34)	.62 (.56-.69)/ .58 (.54-.62)
Anxiety Sensitivity	4,263/5,345	6.09 (4.82), 0-36/ 9.43 (6.17), 0-35	1.40/.94	.38 (.35-.41)/ .42 (.39-.45)	.20 (.17-.24)/ .19 (.16-.23)	.35 (.18-.43)/ .32 (.19-.42)	.04 (.00-.17)/ .10 (.02-.20)	.61 (.55-.67)/ .58 (.54-.63)

Table A1 (continued) – Descriptive statistics, cross twin correlations and univariate results separately for males and females.

Notes:

SD – standard deviation, *MZ* – monozygotic, *DZ* – dizygotic, *A*-additive genetic parameters, *C*- shared environmental parameters, *E* – non-shared environmental parameters.

Total sample zygosity was 14.71% MZ male, 20.50% MZ female, 13.80% DZ male, 18.24% DZ female, 31.72% DZ opposite-sex, 1.03% unknown.

Descriptive statistics and cross twin correlations are presented on untransformed and unregressed variables for comparison with other published samples. Univariate analyses are presented on transformed variables.

95% Confidence Intervals (CIs) are presented in brackets. CIs not including 0 indicate significant estimates. Non-overlapping CIs mean significant difference between the values. Mindfulness was measured only in a subset of twins (a cohort born between January 1994 to August 1994), while depression and anxiety sensitivity was measured in the whole sample, resulting in larger sample sizes. All twins were approximately 16 years old at the time of data collection.

Table A2 - Multivariate results separately for males and females – phenotypic, genetic and non-shared environmental correlations, and proportion of phenotypic correlation explained by A, C and E.

	Cross twin cross trait correlations (males/females)		Phenotypic, Genetic and Environmental Correlations (males/females)				Proportion of the phenotypic correlation explained by A, C and E (males/females)		
	r_{MZ}	r_{DZ}	r_{ph}	r_A	r_c	r_E	A	C	E
Mindfulness-Depression	.13 (.02-23)/ .20 (.11-.29)	.12 (.04-.20)/ .02 (-.05-.09)	.31 (.26-.37)/ .35 (.31-.39)	.58 (.24-.92)/ .94 (.60-1.00)	.29 (-1.00-1.00)/ -.07 (-1.00-1.00)	.19 (.06-.30)/ .23 (.15-.31)	.58 (.66-.88)/ .59 (.20-.77)	.05 (.00-.45)/ .00 (.00-.33)	.38 (.12-.63)/ .42 (.27-.57)
Mindfulness-Anxiety Sensitivity	.10 (-.01-21)/ .19 (.10-.28)	.19 (.11-.27)/ .02 (-.05-.09)	.31 (.24-.37)/ .36 (.31-.40)	.54 (.06-.81)/ .65 (.32-.97)	.89 (-1.00-1.00)/ .65 (-1.00-1.00)	.14 (.01-28)/ .27 (.17-.36)	.60 (.43-.96)/ .59 (.42-.82)	.12 (.00-.55)/ .00 (.00-.21)	.29 (.01-.57)/ .47 (.30-.64)
Depression-Anxiety Sensitivity	.22 (.17-.27)/ .28 (.24-.32)	.16 (.12-.20)/ .15 (.12-.18)	.46 (.44-.49)/ .49 (.47-.51)	.67 (.83-.92)/ .71 (.39-.97)	.69 (-1.00-1.00)/ .80 (.47-1.00)	.34 (.28-.40)/ .36 (.31-.40)	.46 (.16-.63)/ .32 (.13-.50)	.08 (.00-.34)/ .26 (.11-.42)	.45 (.36-.56)/ .42 (.36-.49)

Table A2 (continued) - Multivariate results separately for males and females – phenotypic, genetic and non-shared environmental correlations, and proportion of phenotypic correlation explained by A, C and E.

Notes:

MZ – monozygotic, *DZ* – dizygotic, r_{ph} – phenotypic correlation, r_A – genetic correlation, r_E – shared environmental correlation, r_E – non-shared environmental correlation, *A* - additive genetic parameters, *C* – shared environmental parameters, *E* – non-shared environmental parameters.

95% Confidence Intervals (CIs) are presented in brackets. CIs not including 0 indicate significant estimates. Non-overlapping CIs mean significant difference between the values.

Table A3– Multivariate results for the full ACE model – phenotypic, genetic and environmental correlations, and proportion of phenotypic correlation explained by A, C and E.

	Phenotypic, Genetic and Environmental Correlations				Proportion of the phenotypic correlation explained by A, C and E		
	r_{ph}	r_A	r_C	r_E	A	C	E
Mindfulness-Depression	.34 (.30-.37)	.63 (.29-1.00)	.22 (-1.00-1.00)	.22 (.14-.29)	.56 (.23-.87)	.03 (.00-.28)	.41 (.26-.55)
Mindfulness-Anxiety Sensitivity	.34 (.30-.38)	.52 (.26-.75)	.68 (-1.00-.1.00)	.23 (.15-.30)	.52 (.20-.77)	.06 (.00-.29)	.42 (.27-.58)
Depression-Anxiety Sensitivity	.48 (.47-.50)	.65 (.51-.80)	.86 (.03-1.00)	.35 (.31-.39)	.44 (.29-.59)	.13 (.02-.25)	.43 (.37-.49)

Table A3 (continued)– Multivariate results for the full ACE model – phenotypic, genetic and environmental correlations, and proportion of phenotypic correlation explained by A, C and E.

Notes:

MZ – monozygotic, *DZ* – dizygotic, r_{ph} – phenotypic correlation, r_A – genetic correlation, r_C –shared environmental correlation, r_E – non-shared environmental correlation, *A* - additive genetic parameters, *C* - shared environmental parameters, *E* – non-shared environmental parameters.

95% Confidence Intervals (CIs) are presented in brackets. CIs not including 0 indicate significant estimates. Non-overlapping CIs mean significant difference between the values.

APPENDIX E –CHAPTER 7 SUPPLEMENTARY MATERIALS

Table E1 – Mean RT on face tasks where array comprised of all female vs all male faces, presented separately for no-distractor and distractor trials.

	No-distractor trials	Distractor trials
Face colour		
RT on array where all faces are female	2804.95	3171.86
RT on array where all faces are male	2871.59	3409.86
Face valence		
RT on array where all faces are female	2847.10	2932.84
RT on array where all faces are male	2947.88	3277.71

Notes:

On all female arrays, the target was the odd male face. On all male arrays, the target was the odd female face. The distractor was the same sex as the array but either had opposite colour (faces-colour task) or opposite valence (faces-valence task).

Repeated measures ANOVA indicated that there were significant differences between mean RT:

Face colour: F=(2.58, 128.41, Huynh-Feldt correction)=48.26, p<.001, η_p^2=.49. There was no significant difference between males and females on no-distractor trials (p=.52), which suggests that it doesn't matter whether the target is male or female. However on distractor trials performance on the 'male' array was slower than on the 'female' array (p=.02). This suggests that the male colour distractor was more distracting than the female colour distractor. Both female and male colour distractors produced slower RTs as compared to no-distractor trials.

Face valence: F=(2.29, 123.71, Huynh-Feldt correction)=21.05, p<.001, η_p^2=.28. There was no significant difference between males and females on no-distractor trials (p=.38) , suggesting that it doesn't matter whether the target is male or female. However on distractor trials performance on the 'male' array was

slower than on the ‘female’ array (p=.00). This suggests that the male valence distractor was more distracting than the female valence distractor. In this task we also found that RTs on female valence distractor trials were had not significantly slower than RTs on no-distractor female trials (p=.53).